Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Brott TG, Hobson RW II, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med 2010;363:11-23. DOI: 10.1056/NEJMoa0912321.

(PDF last updated June 30, 2010.)

Supplementary Appendix

- Section 1. Additional Study Results
- Section 2. CREST Investigators and Research Coordinators (The center Principal Investigator is listed in the primary article.)
- Section 3. CREST Study Protocol, Statistical Analysis Plan

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Stenting Compared to Endarterectomy for Treatment of Carotid Artery Stenosis

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SECTION 1. Additional Study Results

Table 1. Summary of antiplatelet and anticoagulant therapy for CAS and CEA.

All Carotid Stent Patients				
Medication	**Pre-Procedure**	**Intra-Procedure**	**Post-Procedure**	**Post Discharge**
Heparin[1]	PRN	Maintain ACT 250-300 sec.[1]	PRN[2]	None
Aspirin	325 mg po bid[2] (Begin 48 hours before)	None	325 mg[3] 1-2 tablets po daily for 30 days	325 mg [3,4] 1 tablet po daily thereafter
Clopidogrel	75 mg po bid daily (Begin 48 hours before)	None	75 mg 1 tablet po daily for 4 weeks	--
Ticlopidine (instead of clopidogrel)	250 mg po bid (Begin 48 hours before)	None	250 mg 1 to 2 tablets po daily for 4 weeks	--
All Carotid Endarterectomy Patients				
Forty-eight hours pre-procedure patients received antiplatelet therapy consisting of aspirin 325 mg po daily. These patients were to remain on aspirin 325 mg daily indefinitely (at least one year). For those patients intolerant at this dose, acceptable alternatives included ticlopidine 250 mg bid, clopidogrel 75 mg po qd, aspirin 81 mg po daily, or aspirin/extended-release dipyridamole bid.				

[1]Bivalirudin could be substituted for heparin. Use was in accordance with manufacturer's instructions. ACT's were not collected when bivalirudin was used as the procedural anticoagulant.

[2]Heparin was given post-procedure as needed.

[3]Could be substituted with 81 mg tablet if patient could not tolerate 325 mg dosage.

[4]After four weeks could be substituted with aspirin/extended release dipyridamole bid or clopidogrel.

Table 2. Description of the study population by treatment allocation in symptomatic patients.

	CAS (n = 668)	CEA (n = 653)
Age – yrs. (mean ± SD)	68.8 ± 9.7	68.8 ± 9.3
Male - %	64.1	65.4
White -%	91.5	91.9
Risk factor status		
Hypertension - %	83.6	84.4
Diabetes - %	28.7	27.5
Dyslipidemia - %	76.9	81.1
Current smoker - %	26.8	29.6
Prior cardiovascular disease - %	36.6	39.3
Prior coronary artery bypass - %	16.8	17.0
SBP (mean ± SD) mmHg	141.7 ± 20.4	140.5 ± 20.5
DBP (mean ± SD) mmHg	74.3 ± 11.9	74.6 ± 11.3
Randomization percent stenosis		
Moderate (<70%)	18.3	21.0
Severe (≥70%)	81.7	79.0
Stenosis Status		
Left carotid treated - %	54.5	52.8
Contralateral occlusion - %	3.2	3.8
Time from randomization to treatment		
Median – days	4	5
Characteristics of Treatments		

Carotid endarterectomy		
General anesthesia - %	--	92.3
Surgical technique - %		
Patch	--	57.0
Shunt	--	59.7
Medical treatment pre-procedure - %		
Aspirin 48 hours	--	92.3
Medical treatment during procedure - %		
Vasopressors	--	64.9
Medical treatment post-procedure - %		
Antiplatelet therapy	--	85.0
Carotid stenting		
Target lesion length – mm (mean ± SD)	17.4 ± 8.8	--
Total length of stented segment – mm (mean ± SD)	34.1 ± 7.3	--
Balloon angioplasty pre-procedure - %	64.0	--
Embolic protection - %	94.5	--
Medical treatment pre-procedure - %		
Antiplatelet therapy 48 hours	96.7	--
Medical treatment during procedure - %		
Heparin	90.3	--
Bivalirudin	9.7	--
Vasopressors	31.5	--
Medical treatment post-procedure - %		
Antiplatelet therapy	98.1	--

Table 3. Description of the study population by treatment allocation in asymptomatic patients.

	CAS (n = 594)	CEA (n = 587)
Age – yrs. (mean ± SD)	69.0 ± 8.0	69.6 ± 8.1
Male - %	63.8	67.5
White -%	94.4	95.4
Risk factor status		
Hypertension - %	88.2	87.9
Diabetes - %	32.6	33.7
Dyslipidemia - %	89.7	91.1
Current smoker - %	26.1	22.2
Prior cardiovascular disease - %	48.6	50.9
Prior coronary artery bypass - %	23.5	26.5
SBP (mean ± SD) mmHg	141.6 ± 19.9	142.0 ± 20.6
DBP (mean ± SD) mmHg	73.6 ± 11.2	73.3 ± 11.6
Randomization percent stenosis		
Moderate (<70%)	7.2	8.2
Severe (≥70%)	92.8	91.8
Stenosis Status		
Left carotid treated - %	46.3	51.6
Contralateral occlusion - %	2.3	2.7
Time from randomization to treatment		
Median – days	8	9
Characteristics of Treatments		

Carotid endarterectomy		
General anesthesia - %	--	87.5
Surgical technique - %		
Patch	--	68.5
Shunt	--	53.6
Medical treatment pre-procedure - %		
Aspirin 48 hours	--	91.8
Medical treatment during procedure - %		
Vasopressors	--	56.6
Medical treatment post-procedure - %		
Antiplatelet therapy	--	96.9
Carotid stenting		
Target lesion length – mm (mean ± SD)	18.2 ± 8.2	--
Total length of stented segment – mm (mean ± SD)	34.7 ± 7.2	--
Balloon angioplasty pre-procedure - %	71.9	--
Embolic protection - %	97.9	--
Medical treatment pre-procedure - %		
Antiplatelet therapy 48 hours	98.7	--
Medical treatment during procedure - %		
Heparin	83.7	--
Bivalirudin	16.3	--
Vasopressors	28.4	--
Medical treatment post-procedure - %		
Antiplatelet therapy	99.8	--

Table 4. Selected risk factor assessments by treatment group.

	CAS	CEA
	Mean or %	Mean or %
Low-density lipoproteins - mg/dl		
Baseline	95.9	95.8
12 Month	89.8	88.3
24 Month	87.9	87.1
36 Month	90.0	86.3
48 Month	88.6	89.1
High-density lipoproteins - mg/dl		
Baseline	43.9	43.3
12 Month	46.6	45.5
24 Month	45.5	45.2
36 Month	46.0	45.3
48 Month	44.8	47.3
Systolic blood pressure - mmHg		
Baseline	141.6	141.2
12 Month	138.0	137.6
24 Month	136.0	137.7
36 Month	137.2	137.2
48 Month	136.3	137.5

Systolic blood pressure >140 mmHg - %		
Baseline	47.2	46.4
12 Month	39.4	38.2
24 Month	33.9	37.5
36 Month	34.8	37.4
48 Month	34.7	37.4
Systolic blood pressure >160 mmHg - %		
Baseline	16.2	16.4
12 Month	11.0	11.5
24 Month	9.6	11.4
36 Month	11.6	10.1
48 Month	9.4	10.8
Diastolic blood pressure - mmHg		
Baseline	74.0	73.9
12 Month	74.2	74.1
24 Month	73.5	73.7
36 Month	74.5	73.6
48 Month	73.6	72.4
Current Smoker - %		
Baseline	26.4	26.1
12 Month*	23.5	19.4
24 Month*	21.8	17.6
36 Month	19.6	16.4

48 Month*	21.8	13.8

*p<0.05 for difference by treatment group

Table 5. Primary endpoint and other endpoint events - symptomatic status and sex by treatment interaction.

	Symptomatic status by treatment interaction (p-value)		Sex by treatment interaction (p-value)	
	Peri-procedural Period[1]	Four-year Period (Includes peri-procedural period)	Peri-procedural Period[1]	Four-year Period (Includes peri-procedural period)
MI Endpoint	0.76		0.16	
Stroke Endpoint (any stroke within peri-procedural[1] period + post-procedural[1] ipsilateral stroke)	0.86	0.38	0.19	0.65
Stroke ± Death Endpoint (any stroke or death within peri-procedural[1] period + post-procedural[1] ipsilateral stroke)	0.98	0.45	0.28	0.79
Primary Endpoint (any stroke, MI or death within peri-procedural[1] period + post-procedural ipsilateral[1] stroke)	0.57	0.84	0.064	0.34

Footnotes

1. Peri-procedural period defined per protocol as 30 days post-procedure for all patients receiving assigned therapy within 30 days from randomization, or 36 days after randomization for all patients not receiving assigned treatment within 30 days

Table 6. Serious adverse events during the peri-procedural period, excluding stroke, myocardial infarction, and death.

Category	CAS	CEA
Surgical Wound Complication		
Hematoma requiring treatment	0	19
Other	3*	20
Bleeding Events**		
Transfusion required	24	12
Hematoma requiring treatment	8	0
Retroperitoneal hemorrhage	4	0
Bleeding moderate	4	2
Bleeding minor	5	1
Femoral Artery Complications, non-hemorrhagic	10	3
Hypotension***	53	24
Hypertension	17	55
Bradycardia		
Requiring permanent pacemaker	6	0
Atropine or no treatment	35	6
Target Lesion Revascularization	10	6

*Patients randomized to CAS who underwent endarterectomy.

**Categories not mutually exclusive.

***Systolic BP ≤80 mmHg or pressors administrated ≥24 hours.

Table 7. Post hoc analysis of the relationship between medical specialty and risk of primary outcome in patients undergoing CAS.

Specialty	HR (95% CI) crude	HR (95% CI) adjusted for age, sex, symptomatic status
Cardiology	reference	reference
Neuroradiology/Neurointerventionist	1.37 (0.69-2.72)	1.27 (0.63-2.54)
Interventional Radiology	0.83 (0.37-1.86)	0.72 (0.32-1.63)
Vascular Surgery	1.02 (0.52-2.00)	1.18 (0.60-2.31)
Neurosurgery	1.72 (0.91-3.28)	1.49 (0.76-2.89)
p-value for difference	0.344	0.505

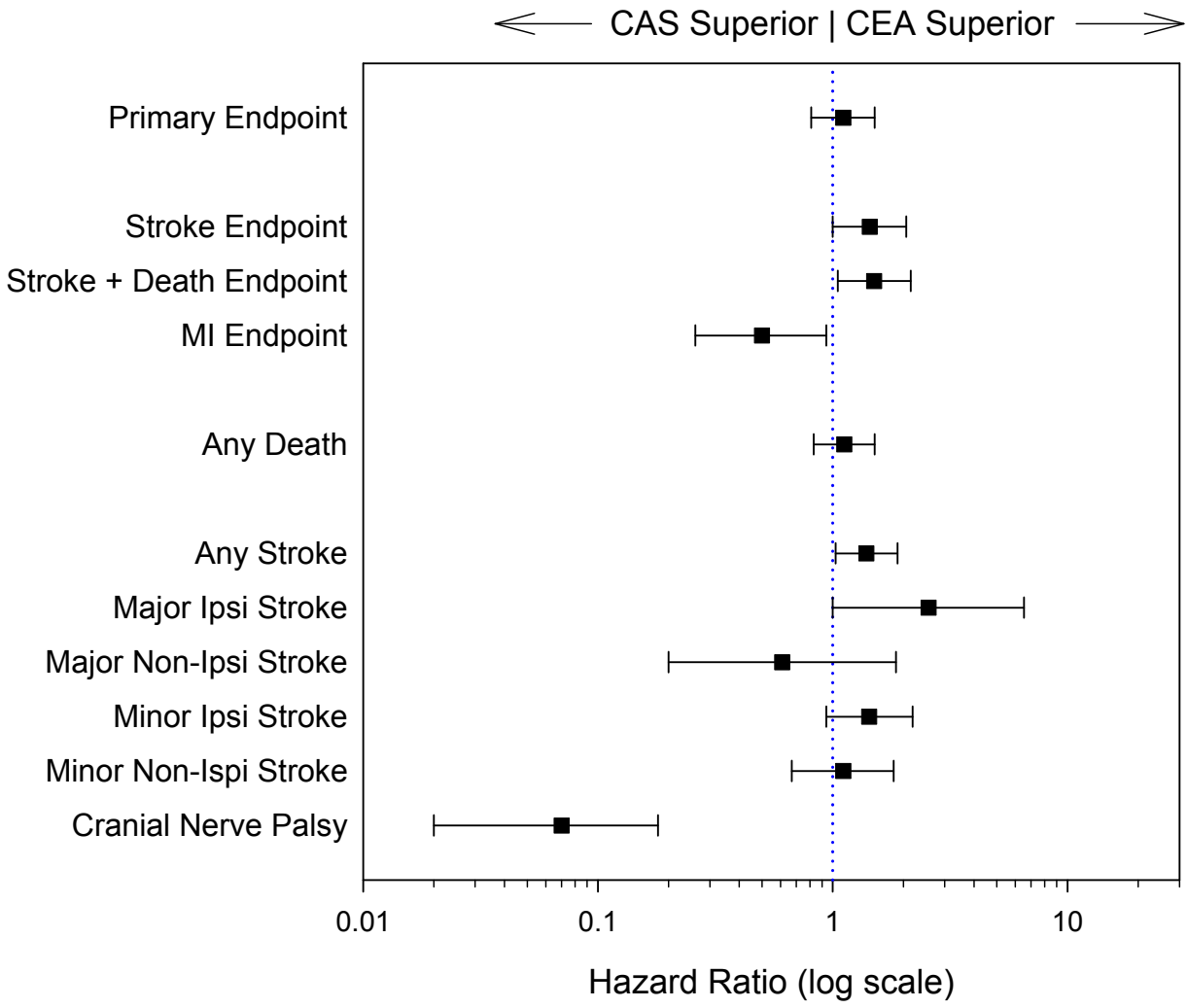

Figure 1. Hazard ratios (and associated 95% confidence intervals) for the primary endpoint and selected efficacy and safety endpoints comparing CAS vs. CEA.

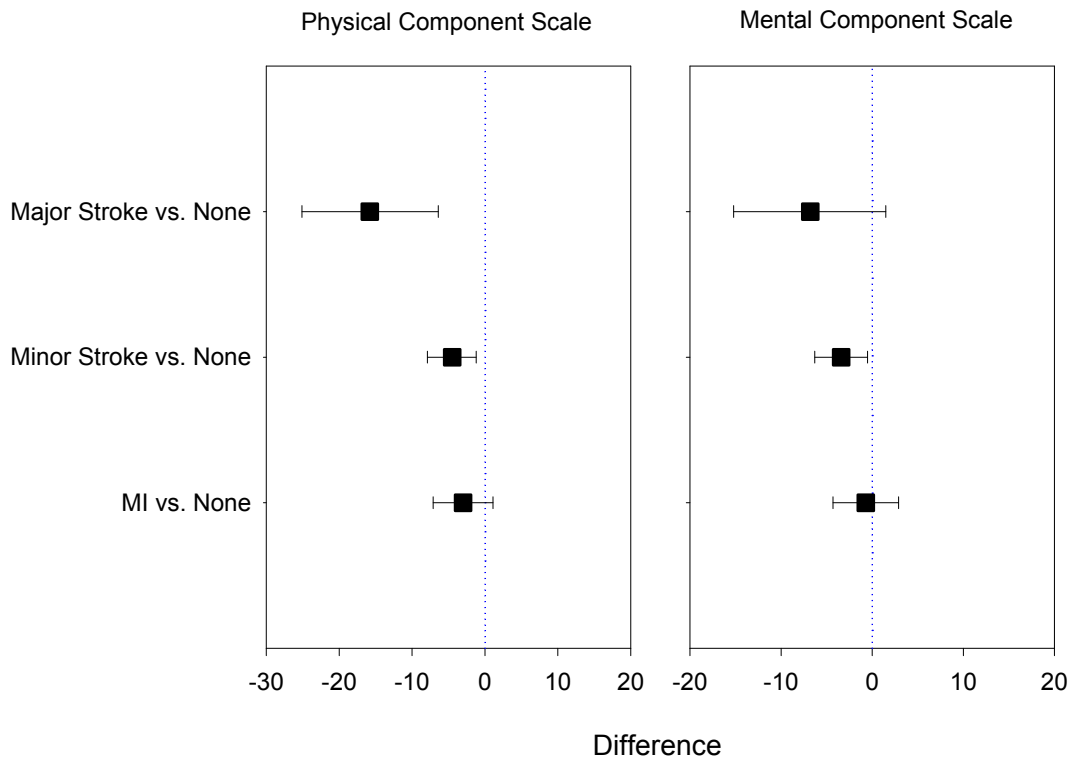

Figure 2. Estimated impact of peri-procedural events (stroke, MI) on the SF-36 physical and mental component summary scales at 1 year based on random effect growth curve models adjusting for age, sex, symptomatic status, and baseline SF-36 measures.

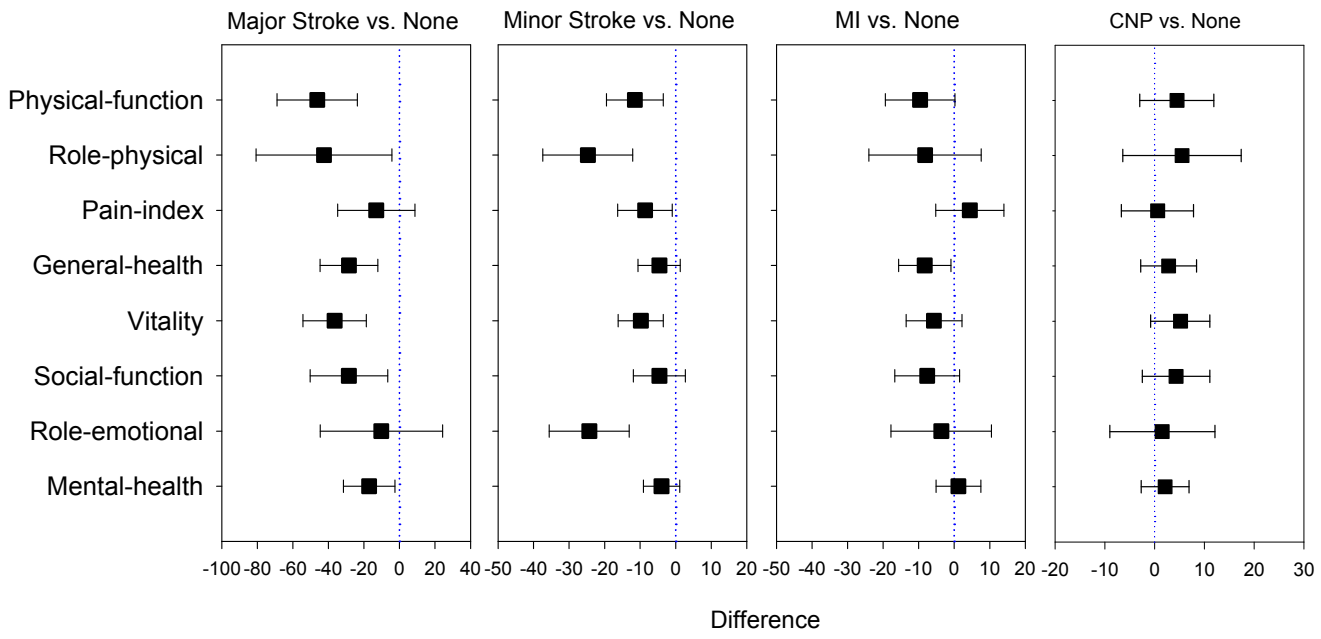

Figure 3. Estimated impact of peri-procedural events on the individual SF-36 subscales at 1 year based on growth curve models adjusting for age, sex, symptomatic status, and baseline health status.

SECTION 2. CREST Investigators and Research Coordinators

The CREST Interventionists, Surgeons, Neurologists, and Research Coordinators (respectively), by Center are listed below (in order of decreasing number of patients who were randomly assigned to a treatment group). At many CREST Centers more than one Interventionist, Surgeon, Neurologist, and Research Coordinator participated. The list below includes only one from each of those categories.

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SECTION 3. CREST Study Protocol

The plans for cost-effectiveness analyses have been redacted from this published version of the protocol.

The statistical analysis plan is described in the study protocol Section 7.0 STATISTICAL METHODS, pages 46 – 49. Details are provided in APPENDIX E, pages 95-113 of the protocol.

PROTOCOL 99–705

CAROTID REVASCULARIZATION ENDARTERECTOMY

VS. STENTING TRIAL (CREST)

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Amendment V July 30, 2007

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Surgical Management Committee:	Wesley Moore, M.D.
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PROTOCOL SUMMARY

Design:	Non-randomized lead-in/credentialing phase Prospective, randomized, parallel, two-arm, multi-center trial, with blinded endpoint evaluation
Enrollment:	1. Lead-in/credentialing phase of approximately 20 subjects per interventionalist 2. Randomized Clinical Trial (RCT) of up to 2,500 subjects
Clinical Site Locations:	Approximately 115 sites in North America
Time Course:	IDE filing: March 2000 Lead-in/credentialing phase: November 2000 Initial randomized enrollment: December 2000 Enrollment complete: TBD Twelve month follow-up complete: TBD
Purpose:	To contrast the relative efficacy of Carotid Artery Stenting (CAS) versus Carotid Endarterectomy (CEA) in preventing stroke, myocardial infarction, and death during a 30-day peri-procedural period, and stroke ipsilateral to the study artery over the follow-up period in patients with symptomatic and asymptomatic extracranial carotid stenosis.
Primary Analyses (NIH Analysis):	Differential efficacy on the composite of stroke, myocardial infarction, and death during a 30-day peri-procedural period and stroke ipsilateral to the study artery during the follow-up period.
Secondary Analyses (NIH Analysis):	1. Differential efficacy of CAS and CEA in male and female patients 2. Contrast peri-procedural (30-day) morbidity and post-procedural (after 30-days) morbidity and mortality 3. Estimate and contrast the morphology of the treated segment at 6 months and 1 year for the two procedures 4. Evaluate differences in measures of health related quality of life and cost effectiveness 5. Identify subgroups of participants at differential risk for CAS and CEA
Primary Analyses (Regulatory Agency Analysis):	Treatment differences in 1-year composite endpoint (stroke, myocardial infarction, and death during a 30-day peri-procedural period and stroke ipsilateral to the study artery between 31 days and 1 year).
Secondary Analyses (Regulatory Agency Analysis):	1. One-year composite endpoint (similar to the primary endpoint) by strata defined by symptomatic status. 2. Peri-procedural events (e.g. 30-day stroke, myocardial infarction, and death; stroke and death; major stroke and death) 3. Acute Success 4. Target lesion revascularization at 12 month. 5. Access site complications requiring treatment 6. Cranial nerve injury unresolved at 1 and 6 months.

Carotid Revascularization Endarterectomy vs. Stenting Trial

(CREST)

1.0 INTRODUCTION

1.1 BACKGROUND AND SIGNIFICANCE

Stroke is the third most common cause of death in North America with approximately 600,000 new strokes reported annually, of which 150,000 are fatal.[1] Besides mortality, morbidity in the more than 4,000,000 surviving stroke victims is substantial, making stroke the leading cause of disability in the United States. Seventy-five percent of strokes occur in the distribution of the carotid arteries.[2-4] Among strokes of a thromboembolic etiology, carotid occlusive disease is the most common cause.[5] On the average, the inpatient costs for an ischemic cerebral infarction (subtype of stroke potentially prevented by carotid revascularization) are estimated to be between $9,209 and $10,555 with additional costs associated with the subsequent disability.[6] In the United States, in 1993, the annual cost for care of stroke victims was estimated to be $30 billion, $17 billion of which was direct medical costs.[7]

1.2 CAROTID ENDARTERECTOMY (CEA)

Carotid endarterectomy, performed with a low peri-procedural complication rate, is the only form of mechanical cerebral revascularization for which definitive evidence of clinical effectiveness has been reported. It has been established as the preferred method of management for select patients with high-grade symptomatic and asymptomatic carotid stenoses.[8-12] The North American Symptomatic Carotid Endarterectomy Trial (NASCET), a randomized controlled clinical trial of endarterectomy and medical therapy versus medical therapy alone, reported CEA and best medical therapy were superior to medical therapy alone in reducing the incidence of stroke alone as well as stroke and death in select patients with symptomatic carotid stenosis (≥70%).[8] Life-table estimates of the cumulative risk of stroke at two years were 26% in the medical group vs. 9% in the surgical group (absolute risk reduction (±SE): 17±3.5%, $p<0.001$). The corresponding estimates for major or fatal ipsilateral stroke were 13.1% vs. 2.5% (absolute risk reduction (±SE): 10.6±2.6%, $p<0.001$) and for any stroke or death were 32% vs. 16% (absolute risk reduction (±SE): 16.5±4.2%, $p<0.001$). Complementary findings were reported in the European Carotid Surgery Trial (ECST) and the Veterans Affairs (VA) symptomatic endarterectomy trial.[11,12] Although, recent presentation of data by the NASCET Investigators on patients with symptomatic disease also has confirmed efficacy of CEA in male patients with 50-69% stenosis, the effect is questionable in women with the same degree of stenosis.[13]

Results from the VA trial on asymptomatic carotid stenosis demonstrated that CEA reduced the incidence of all neurological events, while the Asymptomatic Carotid Atherosclerosis Study (ACAS) confirmed its effectiveness for reduction in ipsilateral stroke and any peri-procedural stroke or death in asymptomatic patients with ≥60% stenoses.[9,10] In ACAS, after a median follow-up of 2.7 years, the aggregate risk over 5 years for ipsilateral stroke and any peri-procedural stroke or death was estimated to be 5.1% for surgical patients and 11% for patients treated medically (aggregate risk

reduction: 53%, 95% CI, 22% to 72%). These trials provide the basis of the current indications for carotid endarterectomy throughout this country and abroad. Because the patients included in the above referenced trials represent a select subset and surgeons were highly skilled with documented low complication rates, the results do not necessarily reflect the true complication rates for the general population with high grade stenosis or high surgical risk.

Of increasing concern is the possibility of a differential efficacy of CEA and possibly Carotid Artery Stenting (CAS) between genders. In patients with high-grade asymptomatic stenosis reported by ACAS, CEA offered a 66% reduction in events over a five-year period for men, but only a 17% reduction for women.[10] In NASCET, while no differential gender effects were reported among symptomatic patients with stenosis greater than 70%, male patients demonstrated greater benefit after CEA than women for stenoses of 50-69%.[13] While the causes for these examples of differential efficacy between genders are not well understood, the effect may be attributed to a higher complication rate for CEA in women, possibly caused by their reported smaller arterial sizes and a greater surgical morbidity. Unfortunately, neither ACAS nor NASCET suspected the possibility of a differential gender effect, and as such did not provide design parameters to evaluate the possibility of a differential gender effect. However, given the results of these two major randomized clinical trials (RCTs) of endarterectomy providing similar findings, a requirement for *a priori* plans to evaluate the possibility of a differential gender effect is incumbent in subsequent trials of the management of carotid atherosclerosis.

1.3 CAROTID ARTERY STENTING (CAS)

Morris et al.[14] reported the first balloon dilatation of a carotid artery in 1968. Kerber[15] and colleagues performed the first human carotid artery dilatation of an atherosclerotic lesion in 1980, and demonstrated that atherosclerotic lesions of the carotid artery could be dilated without necessarily provoking symptomatic atherothromboembolism. Retrospective case reports and case series comprise the bulk of the published literature on carotid angioplasty stenting.[16-40] These reports demonstrated that dilatation of the carotid artery could be performed without necessarily provoking symptomatic cerebral embolization.[16] Subsequent case reports demonstrated the technical feasibility of cerebral angioplasty in selected patients, as well as effectiveness with regard to surrogate endpoints such as, post-dilatation increase in translesional blood flow, regional cerebral blood flow, and cerebral hemodynamics.[41-43] The first report of a multi-center prospective protocol-based study of percutaneous carotid transluminal angioplasty was published in 1993. Despite inferential limitations concerning the clinical effectiveness of carotid angioplasty and CAS, retrospective reports have perpetuated interest in these procedures.

There are several on-going prospective, protocol-based cerebral angioplasty-stent studies.[44-47] In Europe, the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) is attempting to compare surgical intervention and angioplasty for treatment of carotid and vertebral occlusive lesions.[46] The largest multi-center prospective experience in cerebral percutaneous transluminal angioplasty (CPTA) comes

from the North American Cerebral Percutaneous Transluminal Angioplasty Register (NACPTAR).[44,48] Published NACPTAR results provide preliminary evidence concerning the immediate angiographic success and clinical complications, as well as the restenosis rate and predictors of angiographic success for cerebral angioplasty in symptomatic patients with stenosis ≥70%, particularly for patients who were deemed to be poor candidates for CEA.[44,48,49] Interim results were reported on 165 angioplasties in 147 symptomatic non-surgical patients.[44,48] The average stenosis pre-CPTA was 84% (range: 70% to 99%). The average stenosis immediately post-angioplasty was 37% ($p < 0.01$). This corresponded to an immediate success rate of 83% (95% CI, 76% to 88). Death from all causes occurred in 3% of procedures, and stroke in an additional 6%. The 30-day combined rate of death and stroke from all causes was 9% (95% CI, 5 to 15%).[44] Data concerning the rate of restenosis in 44 lesions with angiographic follow-up at a mean of 260 days also has been reported.[49] Of the 37 lesions that were ≤ 70% after the initial dilatation, restenosis occurred in 8 (22%; 95% CI, 10-38%). Of the patients who had restenosis 5/8 (63%) were symptomatic at the time of follow-up. Cox proportional hazards modeling demonstrated that symptoms and the degree of stenosis pre-CPTA were independent predictors of angiographic restenosis in follow-up. In 1996, Diethrich, Ndiaye, and Reid reported results of carotid angioplasty-stenting in 110 symptomatic patients with ≥70% stenoses from a single institution.[39] One procedure failed (0.9%) for technical reasons and was converted to CEA. Two deaths (1.8%) were observed (one from stroke and one due to a cardiac event). Seven strokes (two major, 1.8% and five minor, 4.5%) and five transient neurological events (4.5%) occurred.

A larger prospective protocol-based study of CAS in 231 patients (271 procedures) was reported by Roubin and colleagues.[50,51] Sixty percent (139) of the patients were symptomatic. Of the arteries treated, 214 (79%) were excluded by NASCET and ACAS criteria. In the first 204 patients reported, ages ranged from 36 to 86 years, and 75% had significant coronary artery disease. Of the initial 238 arteries treated (204 patients), 145 arteries (61%) presented in patients with ipsilateral symptoms (60 strokes, 85 TIAs), while 93 arteries were treated in asymptomatic patients. Nine percent of the patients had an occluded contralateral carotid artery and 15% had restenosis following prior CEA. Eighteen percent of the patients had complex lesions with ulcerated plaques. Technical success was achieved in 99% of patients. In two patients, the carotid artery could not be accessed via the transfemoral approach. In one patient, the procedure was aborted after the initial angiography was complicated by an air embolism. For the entire patient group, major strokes occurred in two patients (0.9%) and minor strokes were observed in 17 patients (7.4%), however, among NASCET-ACAS eligible patients, only one minor stroke (1.8%) was reported. Predictors of stroke in the overall clinical update included advanced age, lesion severity, and long/multiple lesions. In a recent update on 40 NASCET eligible patients, Gomez, Roubin and co-authors reported one transient neurological event (2.5%), and no deaths, major stroke, or myocardial infarctions.[52] Stent deformation occurred in 14% of balloon-expandable stents deployed. Consequently, only self-expanding stents have been employed by the authors thereafter. As a result of these data, a self-expandable stent has been chosen for use by CREST Investigators.

Conclusions regarding these prospective endovascular carotid interventional data await further review. It appears that in selected patients, CAS can produce a significant decrease or eliminate the extracranial carotid stenosis with periprocedural complications comparable to those reported for CEA.

1.4 ASYMPTOMATIC CAROTID ARTERY DISEASE (INCLUSION OF ASYMPTOMATIC PATIENTS IN CREST)

The prevalence of asymptomatic carotid stenosis (>50% by ultrasound) among adults over age 65 has been reported to be as high as 8% in the US population[53-55] with estimates that over two million people in North America are affected [56-58]. The relative risk for ischemic stroke in patients with asymptomatic carotid disease is 2.0[53,59]. Currently, approximately two thirds or more of carotid intervention procedures (either CEA or CAS) are being performed for asymptomatic carotid stenosis. This number is likely to increase based on the recently published results from the Asymptomatic Carotid Surgery Trial (ASCT) [60]. This randomized trial evaluating 3120 asymptomatic patients, (with 60% or greater stenosis by ultrasound) randomized to immediate CEA or indefinite deferral of CEA demonstrated that immediate CEA nearly halved the net 5-year stroke risk from 11.7% to 6.4%. Half of this 5-year benefit involved disabling or fatal strokes. Among the patients treated with immediate CEA in this trial, those with <80% diameter stenosis on ultrasound (mean 69%) appeared to benefit about as much as those with greater degrees of stenosis. These results expand upon the prior positive results for CEA demonstrated in the ACAS trial [9, 10].

Application of carotid stenting in asymptomatic patients is currently under evaluation in the US under FDA approved protocols, but experience has been limited primarily to asymptomatic patients considered high risk for surgical endarterectomy (based on clinical comorbidities or anatomic limitations for surgical access). Thus far, results of CAS from these trials evaluating the asymptomatic carotid artery disease patient population, specifically, have been selectively reported. Results reported for the SAPPHIRE trial, a randomized trial evaluating CAS and CEA in a high-risk patient population, indicated a 30 day rate of death, MI or stroke in asymptomatic patients undergoing stent treatment of 6.7% compared to 11.2% for asymptomatic patients undergoing CEA[61-62]. Within the lead-in phase of CREST, considered a moderate to high-risk patient population, the primary endpoint event rate of stroke, myocardial infarction, and death has been comparable between the symptomatic and asymptomatic patients (4.7% vs. 4.3%, respectively).

Although studies have demonstrated a benefit of the less invasive alternative of stenting over surgical treatment in selected high risk populations; the benefit of CAS in the moderate surgical risk asymptomatic population has not been evaluated. Addition of asymptomatic patients in CREST is necessary, therefore, in order to evaluate CAS in these patients and allow for generalization of CREST results (i.e., overall CEA versus CAS efficacy) to this sizable patient population.

1.5 EMBOLIC PROTECTION

Despite the early success of percutaneous interventional carotid procedures, it has been acknowledged that those procedures are not without risks. One of the risks that may be associated with carotid stenting is the potential for distal embolization and its associated sequelae. After careful review of available device data, the CREST Executive Committee has approved the addition of an embolic protection device (EPD) in the Trial.

Two transcranial Doppler studies support the rationale for the use of EPDs in carotid interventions. McCleary et al[62] conducted research using transcranial Doppler to monitor embolic signals during carotid angioplasty in nine patients. This study demonstrated that embolic signals were detected during guidewire placement, contrast injections and in all patients during balloon inflation and deflation, continuing for three minutes following the last balloon deflation in three patients. Research conducted by Markus et al[63] looked at the use of transcranial Doppler ultrasound to monitor embolic signals in the ipsilateral middle cerebral artery at the time of carotid angioplasty. Results from this study concluded that embolic signals during the procedures are very common although often asymptomatic and occur most often during balloon inflation and contrast injections. The size of embolic particulates, which ranged from greater than 200 to 400μ, may have contributed to the asymptomatic nature of the embolic events. It was demonstrated that embolic events related to the procedure occur out to 48 hours post-procedure, becoming less common out to 36 hours post procedure, with the transcranial Doppler reading at 48 hours below the baseline reading. Qureshi et al[65] also identified a 48-hour post-procedure time frame in which neurological events occurred. In this study of 111 patients, there were 14 events - 4 occurred procedurally and 10 occurred out to 48 hours post-procedure. These post-procedural events may be due to a number of factors related to the procedure itself. These factors include stretching of the media and adventitia, disruption of the plaque burden, endothelial denuding, and the formation of platelet aggregates and thrombus. In ten patients assessed, one patient had a clinically evident neurological procedural event, which resolved at one month. Gomez[64] had published similar low procedural event rates of less than 1% for approximately 400 patients during the time in which embolic protection would be of benefit.

A more recent publication by Manninen et al[66] used cadaver models to evaluate embolic material released during CAS of the internal carotid. Doppler, MRI and histopathic analysis were used to monitor for embolic events and all three methods closely correlated. The histopathologic analysis demonstrated that the embolic material was composed of intimal strips and cellular constituents of the diseased plaque, with the largest potential risk from intimal strips of up to 5 mm in length.

Embolic debris may be composed of different components and sizes dependent on the disease progression and lesion type. In an effort to quantify the debris and correlate the associated risk, Ohki[67] conducted a research study in cadaver models by capturing and measuring debris during simulated carotid stenting treatments. The median number of particles in this study was 15 with a range of 2 to 126. The mean particle size was 338μ ($\pm$ 344μ) with a range of 120 to 1200μ. The maximum particle size and the number of particles generated had a close correlation. There were a higher number of echolucent vs. echogenic particles; with a median of 26 and range of 3 to 126 for the former compared

with a median of 9 and a range of 2 to 73 for the latter. There was also a correlation between percent stenosis and particle number; greater than or equal to 90% stenosis had a median of 17.5 and a range of 6 to 80 particles compared with less than 90% stenosis at a median of 6.5 and range of 2 to 126 particles. The findings in this study concluded that echolucent debris and stenosis of greater than 90% had a higher potential for production of embolic particles.

Reports from two early EPD studies have been encouraging. In 1999, Theron[69] reported on a series of carotid stent procedures in which he used the Wallstent™ and a protection system that employed temporary occlusion of the internal carotid artery followed by "a cleaning procedure prior to its removal." There was a 1.5% embolic complication rate that the author attributed to technical problems or anatomical variations. Parodi et al[60] performed carotid angioplasty and stenting on 46 patients during a 12-month period. Cerebral protection was used in 25 of those patients. The unprotected group had a 9.53% rate of neurologic complications compared with a 0% rate for the group with embolic protection. Although not statistically significant, the authors believe that the results point to the probable effectiveness of EPDs.

As embolic debris associated with internal carotid interventions has been quantified, analyzed and correlated not only to risk but associated embolic events, it has become evident that EPDs may have a place in preventing embolic debris-related events and their clinical sequelae during internal carotid interventions.

1.6 RESEARCH PLAN

1.6.1 STUDY OBJECTIVE

The primary goal of CREST is to assess if the efficacy of CAS differs from that of CEA over a multi-year time horizon. Data from CREST will be used to both provide an assessment of the differential efficacy of CEA and CAS and support a submission to the FDA for an indication for CAS for the subject device. Two separate analyses will be performed for this study. First, a traditional difference assessment as described in the NIH submission, and second an equivalency analysis for submission to the FDA. For complete details of efficacy and primary and secondary endpoints see Section 4.0.

1.6.2 OVERVIEW OF STUDY PLAN/STUDY DESIGN

CREST is a randomized, controlled, clinical trial in symptomatic and asymptomatic patients with extracranial internal carotid stenosis. The Trial will assess the differential efficacy of CAS and CEA in preventing stroke, myocardial infarction, and death in the peri-procedural period and ipsilateral stroke over the follow-up period. This study will enroll approximately 2,500 patients who satisfy entry criteria. Recruitment restrictions will be imposed to ensure that the proportion of symptomatic patients is between 32% and 68% of the total study population at the conclusion of the study. This will be achieved by "closing" recruitment to the stratum (symptomatic or asymptomatic) that reaches the goal first. In this manner, no less than 800 symptomatic or asymptomatic

patients will be treated within CREST to help assure that data collected within CREST are pertinent to patients with either symptomatic or asymptomatic carotid artery disease.

A lead-in phase will include a clinical center start-up and credentialing period, during which each interventionalist planning to perform carotid stenting will perform approximately 20 implants in patients. Results from each interventionalist will be reviewed by the Interventional Management Committee (IMC), with Committee approval being required prior to the interventionalist performing CAS on randomized patients.

For the randomized cohort, overall safety and efficacy will be evaluated by comparing acute and late-term individual and composite endpoints, adverse events, and all Core Laboratory evaluations. The primary endpoints and selected secondary endpoints will be analyzed on an intent-to-treat basis, i.e., each outcome will be attributed to the intended assigned treatment regardless of the actual sequence of procedures or anticoagulation regimens that occur.

2.0 PATIENT SELECTION AND ENROLLMENT

2.1 SELECTION OF PATIENTS

For lead-in patients refer to *Appendix B*- Selection of Lead-In Patients.

If an Investigator is unable to utilize the Embolic Protection Device, it will not exclude or disqualify a patient from participating in CREST.

For use of the EPD within CREST, refer to section 3.1.3 and *Appendix C.*

Candidates for the randomized phase of this trial may have either symptomatic *or* asymptomatic carotid artery stenosis. The ratio of symptomatic to asymptomatic patients recruited by site will be monitored by the Statistical and Data Management Center (SDMC). Patients must meet all of the following criteria.

2.1.1 ELIGIBILITY CRITERIA FOR SYMPTOMATIC PATIENTS

Clinical Inclusions for Symptomatic Patients

1. Patient age ≥18 years old.
2. Symptomatic patient, as evidenced by transient ischemic attack (TIA), amaurosis fugax, minor or non-disabling stroke (in the hemisphere supplied by the target vessel), within 180 days of the randomization date.
3. Patient has no childbearing potential or has a negative pregnancy test within one week prior to the study procedure.
4. Patient, and the patient's physician agree to have the patient return for all required clinical contacts following study enrollment.
5. Patient has been informed of the nature of the study, and has provided written informed consent, approved by the appropriate Institutional Review Board

(IRB)/Medical Ethics Committee (MEC) of the respective clinical site. (Sample consent - *Appendix A*).

6. Patient is a candidate for CEA and meets all other eligibility requirements.

Anatomic Inclusions for Symptomatic Patients

For those patients who have carotid angiography available prior to randomization, the angiogram will be utilized to establish eligibility. If an angiogram is not available, a carotid ultrasound may be sufficient to establish eligibility. (Section 2.2.3)

1. Patient has a discrete lesion located in the internal carotid artery (ICA) (with or without involvement of the contiguous common carotid artery (CCA)).
2. Carotid stenosis ≥50% defined as:
   a) Stenosis ≥70% by ultrasound
   b) Stenosis ≥50% by angiography (based on NASCET Criteria, reference *F*) **or**
   c) If the ultrasound indicates 50-69% stenosis, that patient may be randomized on the basis of results from a CT angiogram (CTA) or MR angiogram (MRA) **IF** a radiologist or neuro-imaging specialist documents his/her opinion that a CTA or MRA indicate ≥ 70% stenosis and that the CTA or MRA is of acceptable technical quality. If the results of the CTA or MRA are not conclusive, the patient should undergo conventional angiography.
3. Target ICA vessel reference diameter must be measured to be ≥4.0 mm and ≤9.0 mm. Target ICA measurements may be made from angiography of the contralateral artery.
4. Patients with bilateral carotid stenosis are eligible. Management of the non-randomized stenosis may be done in accordance with local Principal Investigator (PI) recommendation. *(Note: Treatment of the non-study artery must take place at least 30 days prior to randomization, or >30 days after the study procedure is completed.)*
5. Expected ability to deliver the stent to the lesion (absence of excessive tortuosity).

Clinical Exclusions for Symptomatic Patients

1. Patient has an evolving stroke.
2. Patient has had known untoward reaction to anesthesia not able to be overcome by pretreatment with medications.
3. Patient has history of intolerance or allergic reaction to any of the study medications, including aspirin (ASA), ticlopidine and clopidogrel. (Patients must be able to tolerate a combination of ASA and ticlopidine or ASA and clopidogrel)
4. Patient has active bleeding diathesis or coagulopathy or will refuse blood transfusions.
5. Patient with a history of major ipsilateral stroke likely to confound study endpoints.
6. Patient has severe dementia.

7. Patient has a history of spontaneous intracranial hemorrhage within the past 12 months.
8. Patient has had a recent (<7 days) stroke of sufficient size (on CT or MRI) to place him or her at risk of hemorrhagic conversion during the procedure.
9. Patient had hemorrhagic transformation of an ischemic stroke within the past 60 days.
10. Patient has Hgb <10 g/dl, platelet count <125,000/μl, uncorrected INR >1.5, bleeding time >1 minute beyond upper limit normal, or heparin-associated thrombocytopenia.
11. Patient has any condition that precludes proper angiographic assessment or makes percutaneous arterial access unsafe (e.g., morbid obesity, sustained SBP >180 mm Hg.).
12. Patient has had neurologic illnesses within the past two years characterized by fleeting or fixed neurologic deficit which cannot be distinguished from TIA or stroke (e.g. partial or secondarily generalized seizures, complicated or classic migraine, tumor or other space-occupying brain lesions, subdural hematoma, cerebral contusion or other post-traumatic lesions, intracranial infection, demyelinating disease, moderate to severe dementia, or intracranial hemorrhage).
13. Patient is actively participating in another drug or device trial (IND or IDE) that has not completed the required protocol follow-up period. Patients may be enrolled only once in CREST, and may not participate in any other clinical trial during the CREST follow-up period.
14. Patient has inability to understand and cooperate with study procedures or provide informed consent.
15. Patient has vertebrobasilar insufficiency symptoms only, without clearly identifiable symptoms referable to the study carotid artery.
16. Knowledge of cardiac sources of emboli (e.g. left ventricular aneurysm, intracardiac filling defect, cardiomyopathy, aortic or mitral prosthetic heart valve, calcific aortic stenosis, endocarditis, mitral stenosis, atrial septal defect, atrial septal aneurysm, or left atrial myxoma).
17. Chronic atrial fibrillation.
18. Any episode of paroxysmal atrial fibrillation within the past 6 months, or history of paroxysmal atrial fibrillation requiring chronic anticoagulation.
19. Patient has had a MI within previous 30 days.
20. Patient has had a recent GI bleed that would interfere with antiplatelet therapy.
21. Patient is considered a non-surgical or a high risk surgical candidate defined as the presence of any one or more of the following medical conditions:

a) Knowledge of two or more proximal or major diseased coronary arteries with ≥70% stenosis that have not, or cannot be revascularized.

b) Ejection fraction <30% or New York Heart Association (NYHA) Functional Class III or higher.

c) Unstable angina defined as rest angina with ECG changes.

d) Currently on a list for major organ transplantation (i.e., heart, lung, liver, kidney) or is being evaluated for such.

e) Malignancy or respiratory insufficiency limiting life expectancy to <5 years or FEV_1 <30% (predicted).

f) Dialysis dependent renal failure.

g) Uncontrolled diabetes defined as fasting glucose >400 mg/dl and ketones > +2.

h) Concurrent requirement for any surgery requiring general anesthesia.

22. Patient may be considered a non-surgical candidate for CEA as a result of one or more anatomic conditions or features which preclude normal surgical access (a-f), or a high surgical risk defined as the presence of any one or more anatomic conditions that present an increased potential for adverse events (g-i).

    a) Patient is status/post radiation treatment to the neck.

    b) Patient is status/post radical neck surgery.

    c) Surgically inaccessible lesions (i.e. lesions above level of C2).

    d) Spinal immobility – inability to flex neck beyond neutral or kyphotic deformity.

    e) Symptomatic, well-delineated carotid artery dissection below the carotid siphon.

    f) Ostial lesion of LCCA/RCCA lesion below clavicle.

    g) Presence of tracheostomy stoma.

    h) Contralateral laryngeal nerve paralysis.

    i) Previous carotid endarterectomy, extracranial-intracranial or subclavian bypass procedure ipsilateral to the carotid stenosis.

Anatomic Exclusions for Symptomatic Patients

Specific criteria are for patients who have angiograms available prior to randomization:

1. Severe vascular tortuosity or anatomy that would preclude the safe introduction of a guiding catheter, guiding sheath or stent placement.
2. Presence of a previously placed intravascular stent or graft in the ipsilateral distribution.
3. Presence of extensive or diffuse atherosclerotic disease involving the aortic arch and proximal common carotid artery that would preclude the safe introduction of a guiding catheter or guiding sheath.

4. An intraluminal filling defect (defined as an endoluminal lucency surrounded by contrast, seen in multiple angiographic projections, in the absence of angiographic evidence of calcification) that is not associated with an ulcerated target lesion.
5. Abnormal angiographic findings that constitute a contraindication to CEA: ipsilateral intracranial or extracranial arterial stenosis greater in severity than the lesion to be treated, cerebral aneurysm ≥ 5 mm, AVM (arteriovenous malformation) of the cerebral vasculature, or other abnormal angiographic findings that constitute contraindication to CEA.
6. Bilateral carotid stenosis if intervention is planned within the 30-day CREST periprocedural period.
7. Occlusion [Thrombolysis In Myocardial Infarction Trial (TIMI 0)] "string sign" >1 cm of the ipsilateral common or internal carotid artery.

2.1.2 ELIGIBILITY CRITERIA FOR ASYMPTOMATIC PATIENTS

Clinical Inclusions for Asymptomatic Patients

1. Patient age ≥ 18 years old.
2. Asymptomatic patient with compatible history and findings on physical and neurological exam. Patients with eligible carotid stenosis that do not meet the definition for symptomatic carotid stenosis may be enrolled as asymptomatic patients. This includes those patients with
    a. No prior carotid territory symptoms or
    b. Prior symptoms referable only to the hemisphere contralateral to the target vessel or
    c. Symptoms in either hemisphere > 180 days prior to randomization or
    d. Vertebrobasilar symptoms only

    Note: Within the asymptomatic patient group, patients with prior symptoms (> 180 days) will be identified as "recently asymptomatic"; while patients with no prior symptoms at anytime will be identified as "always asymptomatic".

3. Patient has no childbearing potential or has a negative pregnancy test within one week prior to the study procedure.
4. Patient, and the patient's physician agree to have the patient return for all required clinical contacts following study enrollment.
5. Patient has been informed of the nature of the study, and has provided written informed consent, approved by the appropriate Institutional Review Board (IRB)/Medical Ethics Committee (MEC) of the respective clinical site. (Sample consent - *Appendix A*).
6. Patient is a candidate for CEA and meets all other eligibility requirements.

Anatomic Inclusions for Asymptomatic Patients

For those patients who have carotid angiography available prior to randomization, the angiogram will be utilized to establish eligibility. If an angiogram is not available, a carotid ultrasound may be sufficient to establish eligibility. (Section 2.2.3)

1. Patient has a discrete lesion located in the internal carotid artery (ICA) (with or without involvement of the contiguous common carotid artery (CCA)).
2. Carotid stenosis defined as:
    a) Stenosis ≥70% by ultrasound
    b) Stenosis ≥60% by angiography (based on NASCET Criteria, reference *F*) or
    c) If the ultrasound indicates 50-69% stenosis, the patient may be randomized on the basis of results from a CTA or MRA **IF** a radiologist or neuro-imaging specialist documents his/her opinion that a CTA or MRA indicate ≥ 80% stenosis and that the CTA or MRA is of acceptable technical quality. If the results of the CTA or MRA are not conclusive, the patient should undergo conventional angiography.
3. Target ICA vessel reference diameter must be measured to be ≥4.0 mm and ≤9.0 mm. Target ICA measurements may be made from angiography of the contralateral artery.
4. Patients with bilateral carotid stenosis are eligible. Management of the non-randomized stenosis may be done in accordance with local Principal Investigator (PI) recommendation. *(Note: Treatment of the non-study artery must take place at least 30 days prior to randomization, or >30 days after the study procedure is completed.)*
5. Expected ability to deliver the stent to the lesion (absence of excessive tortuosity).

Clinical Exclusions for Asymptomatic Patients

1. Patient has an evolving stroke.
2. Patient has had known untoward reaction to anesthesia not able to be overcome by pretreatment with medications.
3. Patient has history of intolerance or allergic reaction to any of the study medications, including aspirin (ASA), ticlopidine and clopidogrel. (Patients must be able to tolerate a combination of ASA and ticlopidine or ASA and clopidogrel)
4. Patient has active bleeding diathesis or coagulopathy or will refuse blood transfusions.
5. Patient with a history of major ipsilateral stroke likely to confound study endpoints.
6. Patient has severe dementia.
7. Patient has a history of spontaneous intracranial hemorrhage within the past 12 months.

8. Patient has had a recent (<7 days) stroke of sufficient size (on CT or MRI) to place him or her at risk of hemorrhagic conversion during the procedure.
9. Patient had hemorrhagic transformation of an ischemic stroke within the past 60 days.
10. Patient has Hgb <10 g/dl, platelet count <125,000/μl, uncorrected INR >1.5, bleeding time >1 minute beyond upper limit normal, or heparin-associated thrombocytopenia.
11. Patient has any condition that precludes proper angiographic assessment or makes percutaneous arterial access unsafe (e.g., morbid obesity, sustained SBP >180 mm Hg.).
12. Patient has had neurologic illnesses within the past two years characterized by fleeting or fixed neurologic deficit which cannot be distinguished from TIA or stroke (e.g. partial or secondarily generalized seizures, complicated or classic migraine, tumor or other space-occupying brain lesions, subdural hematoma, cerebral contusion or other post-traumatic lesions, intracranial infection, demyelinating disease, moderate to severe dementia, or intracranial hemorrhage).
13. Patient is actively participating in another drug or device trial (IND or IDE) that has not completed the required protocol follow-up period. Patients may be enrolled only once in CREST, and may not participate in any other clinical trial during the CREST follow-up period.
14. Patient has inability to understand and cooperate with study procedures or provide informed consent.
15. Knowledge of cardiac sources of emboli (e.g. left ventricular aneurysm, intracardiac filling defect, cardiomyopathy, aortic or mitral prosthetic heart valve, calcific aortic stenosis, endocarditis, mitral stenosis, atrial septal defect, atrial septal aneurysm, or left atrial myxoma).
16. Chronic atrial fibrillation.
17. Any episode of paroxysmal atrial fibrillation within the past 6 months, or history of paroxysmal atrial fibrillation requiring chronic anticoagulation.
18. Patient has had a MI within previous 30 days.
19. Patient has had a recent GI bleed that would interfere with antiplatelet therapy.
20. Patient is considered a non-surgical or a high risk surgical candidate defined as the presence of any one or more of the following medical conditions:
    a) Knowledge of two or more proximal or major diseased coronary arteries with ≥70% stenosis that have not, or cannot be revascularized.
    b) Ejection fraction <30% or New York Heart Association (NYHA) Functional Class III or higher.
    c) Unstable angina defined as rest angina with ECG changes.

d) Currently on a list for major organ transplantation (i.e., heart, lung, liver, kidney) or is being evaluated for such.

e) Malignancy or respiratory insufficiency limiting life expectancy to <5 years or FEV_1 <30% (predicted).

f) Dialysis dependent renal failure.

g) Uncontrolled diabetes defined as fasting glucose >400 mg/dl and ketones > +2.

h) Concurrent requirement for any surgery requiring general anesthesia.

22. Patient may be considered a non-surgical candidate for CEA as a result of one or more anatomic conditions or features which preclude normal surgical access (a-f), or a high surgical risk defined as the presence of any one or more anatomic conditions that present an increased potential for adverse events (g-i).

    a) Patient is status/post radiation treatment to the neck.

    b) Patient is status/post radical neck surgery.

    c) Surgically inaccessible lesions (i.e. lesions above level of C2).

    d) Spinal immobility – inability to flex neck beyond neutral or kyphotic deformity.

    e) Symptomatic, well-delineated carotid artery dissection below the carotid siphon.

    f) Ostial lesion of LCCA/RCCA lesion below clavicle.

    g) Presence of tracheostomy stoma.

    h) Contralateral laryngeal nerve paralysis.

    i) Previous carotid endarterectomy, extracranial-intracranial or subclavian bypass procedure ipsilateral to the carotid stenosis.

Anatomic Exclusions for Asymptomatic Patients

Specific criteria are for patients who have angiograms available prior to randomization:

1. Severe vascular tortuosity or anatomy that would preclude the safe introduction of a guiding catheter, guiding sheath or stent placement.
2. Presence of a previously placed intravascular stent or graft in the ipsilateral distribution.
3. Presence of extensive or diffuse atherosclerotic disease involving the aortic arch and proximal common carotid artery that would preclude the safe introduction of a guiding catheter or guiding sheath.
4. An intraluminal filling defect (defined as an endoluminal lucency surrounded by contrast, seen in multiple angiographic projections, in the absence of angiographic evidence of calcification) that is not associated with an ulcerated target lesion.
5. Abnormal angiographic findings that constitute a contraindication to CEA: ipsilateral intracranial or extracranial arterial stenosis greater in severity than the lesion to be treated, cerebral aneurysm ≥ 5 mm, AVM (arteriovenous malformation) of the

cerebral vasculature, or other abnormal angiographic findings that constitute contraindication to CEA.

6. Bilateral carotid stenosis if intervention is planned within the 30-day CREST periprocedural period.
7. Occlusion [Thrombolysis In Myocardial Infarction Trial (TIMI 0)] "string sign" >1 cm of the ipsilateral common or internal carotid artery.

2.2 PATIENT IDENTIFICATION

2.2.1 SCREENING OF SUBJECTS

All clinical sites will have a CREST team consisting of a neurologist, surgeon, interventionalist, experienced ultrasonographer and dedicated Research Coordinator (RC). If the study neurologist is unavailable, the neurological evaluation, including the NIHSS can be performed by an independent neuroscientist/physician certified in the use of the NIHSS. This physician cannot be the one that performs the study procedure on the patient.

The screening and recruitment of potential patients will be conducted by the RC under the direction of the designated PI. It is anticipated that patients will be recruited from three major pools: 1) hospitalized stroke patients; 2) individuals referred to a vascular laboratory for noninvasive assessment of the carotid arterial system; and 3) angiography suites.

Once a patient with suspected carotid artery disease is identified, a chart review will be performed to determine whether ultrasound and/or angiography have been performed. To be considered for enrollment as a **symptomatic** patient, initial screening criteria must demonstrate, by clinical impression, that a non-disabling cerebral infarction (CI), amaurosis fugax, or TIA has occurred within 180 days of the baseline assessment and that the patient has ≥ 70% stenosis by ultrasound (or ≥ 50% stenosis by angiography or ≥ 70% by MRA/CTA if ultrasound demonstrates 50-69% stenosis). To be considered for enrollment as an **asymptomatic** patient, initial screening criteria should demonstrate no disabling stroke, neurologically asymptomatic for a minimum period of 180 days from the time of the baseline assessment and ≥ 70% stenosis by ultrasound (or ≥ 60% stenosis by angiography or 80% by MRA/CTA if ultrasound is between 50-69% stenosis).

2.2.2 DETERMINATION OF SYMPTOMATIC STATUS AT BASELINE

The Questionnaire for Verifying Stroke-Free Status (revised TIA/Stroke Questionnaire), will be administered to each potentially eligible patient by the RC, and each patient will be interviewed and examined by a study neurologist.[70] Patients with cerebral infarction diagnosed solely on the evidence of brain computed tomography are considered to be asymptomatic. A symptomatic patient is defined as having had a TIA, amaurosis fugax, or minor stroke related to the artery to be randomized, occurring within 180 days of the randomization date. An asymptomatic patient is defined as a participant that has: a) No prior carotid territory symptoms **or** b) Prior symptoms referable only to the hemisphere contralateral to the target vessel **or** c) Symptoms in either hemisphere > 180 days prior to randomization **or** d) Vertebrobasilar symptoms only. Within the asymptomatic patient

group, patients with prior symptoms (> 180 days) will be identified as "recently asymptomatic"; while, patients with no prior symptoms at anytime will be identified as "always asymptomatic".

2.2.3 Determination of Stenosis

For lead-in patients, stenosis is determined by angiography as described in *Appendix F*.

Stenosis ≥ 50% or ≥ 60% by angiography has been chosen by the CREST Investigators as the level of severity for randomization for symptomatic and asymptomatic patients respectively. If a patient presents to a CREST site with an adequate quality angiogram, that angiogram will be used to establish eligibility. If an angiogram is not available, a carotid ultrasound may be sufficient to establish eligibility. The ultrasound used to determine percent stenosis for eligibility must be from a CREST-certified ultrasound laboratory. The ultrasound laboratory should be accredited by the Intersocietal Commission for Accreditation of Vascular Laboratories (ICAVL), or American College of Radiology. If ultrasound demonstrates a stenosis ≥ 70%, the patient can be randomized without angiography. Additionally, if an ultrasound indicates 50-69% stenosis, the patient may be randomized on the basis of results from a CTA or MRA. In order for the patient to be randomized on the basis of a CTA or MRA, the CTA or MRA must be of acceptable technical quality and the radiologist or neuro-imaging specialist must document his/her opinion that the CTA or MRA results indicate that following stenosis criteria have been satisfied: ≥ 70% stenosis for a symptomatic patient or ≥ 80% stenosis for an asymptomatic patient. If the results of the CTA or MRA are not conclusive, the patient should undergo conventional angiography.

2.2.4 Recruitment of Women and Minorities

CREST is committed to recruiting a representative number of women and minorities to the study to reflect the prevalence of disease in the population.

Although the other major CEA clinical trials had only a third of their samples women, the CREST Investigators have set the following recruitment goals: 40% for women and 12% for minorities.

2.3 Informed Consent

All patients will undergo laboratory, neurologic, and duplex and/or angiographic evaluation to determine eligibility. If the patient meets all eligibility criteria and the attending/referring physician agrees, the patient should be approached to obtain written informed consent. If the family of the patient is available, they should also be consulted. The background of the proposed study and the benefits and risks of the procedures and study should be explained to the patient. The patient must sign the consent form prior to enrollment. *(Appendix A)* Failure to obtain a signed, informed consent renders the patient ineligible for the study. All enrolled patients will complete the appropriate consent that has been approved by the CREST Executive Committee, the local IRB/MEC, and the device sponsor. Copies of the signed informed consent will be kept in the patient's medical records.

In addition to obtaining a signed CREST consent, a standard informed consent may be obtained for the intervention/operation as prescribed by the participating hospital.

2.4 PROCEDURE FOR RANDOMIZATION

All patients considered for CREST must be evaluated by the study team consisting of the neurologist, interventionalist, a vascular surgeon or neurosurgeon, and the RC. The study team is responsible for verifying that the patient meets all eligibility criteria and has none of the exclusion criteria. Only patients who are eligible, and have been properly consented and signed the informed consent are to be randomized.

Patients will be evenly randomized to one of two treatment arms with each treatment arm having the probability of one-half (p=0.5). Randomization will be stratified by clinical center and symptomatic status, and permuted block randomization will be performed within strata. Because of the relatively small number of patients expected to be recruited at each center, the block size will be randomly chosen from small multiples of 2 (i.e., 2, 4, or 6). The randomization procedure is a web-based procedure supported by the Statistical and Data Management Center (SDMC).

Randomization is not done until the patient, surgeon, and interventionalist are able to schedule the procedure within a two-week period. The team is notified of the randomization assignment, and for CAS, the surgical team must be available to provide surgical back-up.

Written approval for a center to start the randomization phase will be given when all of the site training and certification requirements have been satisfactorily completed.

3.0 INTERVENTIONS

The Interventional and Surgical Management Committees of CREST (IMC and SMC respectively) recognize that equally skilled operators/surgeons vary in their approach to CAS and CEA. Nonetheless, there is general agreement concerning some aspects of these procedures.

3.1 CAS

For patients randomized to the CAS treatment arm, the CAS procedure is to be performed only by a CREST certified study interventionalist. The interventionalist who is responsible for the specific CAS procedure must have been reviewed and approved by the CREST IMC and completed required training and certification. The individual must be the primary operator on the procedure. Under no circumstances is the responsibility for conduct of the CAS, including placement of either the carotid stent system or the embolic protection device, to be delegated to an interventionalist who is not approved by the IMC.

3.1.1 LEAD-IN PHASE AND REQUIREMENTS FOR CERTIFICATION

Before enrolling any patient, study interventionalists without previous experience with the study devices will be required to undergo specific device training. (See Section 11.3.3-5)

There will be up to approximately 20 lead-in patients per interventionalist in this study. Certification to perform CAS in CREST requires successful implantation of the study devices and approval of the IMC.

Safety data derived from the lead-in phase will be analyzed separately. Serious adverse events will be reported, however, these data will not be pooled into the overall RCT data analysis. All lead-in patients will be followed as outlined in section 3.3.1 – Examination Components.

3.1.2 CATHETER INSERTION PROCEDURE

Arterial access must be established by the femoral route using the Seldinger technique. Local anesthesia with sedation is preferred, as general anesthesia has only rarely been required to perform carotid stenting and general anesthesia may mask clinical changes which could be managed. The choice of anesthetic and sedative agents is left to the discretion of the operator. The use of unapproved devices is not allowed.

In patients randomized on the basis of a carotid duplex study, cervical and intracranial angiography will be done at the discretion of the interventionalist using standard techniques including assessment of aortic arch and brachio-cephalic anatomy.

Patients with anatomic exclusions or other angiographic features deemed by the operator to place the patient at increased risk that are discovered after randomization will have the procedure terminated but the participant will remain in the study and followed according to protocol. CEA or medical therapy may be advised based on medical need.

Either bivalirudin (Angiomax®) or heparin may be used for procedural anticoagulation. If heparin is to be used, a 5,000 unit intravenous bolus is recommended prior to passing a catheter into the target vessel to achieve an activated clotting time (ACT) of 250-300 seconds. Repeat 2,000 unit heparin boluses should be administered at 45-minute intervals until stent implantation and post dilatation is complete maintaining the ACT at 250-300 seconds. Patients with known heparin allergy and for whom the use of bivalirudin is contraindicated are excluded from the study.

Pre-treatment with IV atropine (1 mg) is recommended. Availability of a temporary transvenous or trans-thoracic pacemaker in the catheterization laboratory is considered a prerequisite for safe CAS.

Placement of the guidewire and diagnostic catheter tip should be proximal to the target lesion in order to avoid inducing vasospasm, which could interfere with angiographic measurements of the target vessel.

While it is recognized that the majority of endovascular therapists who currently deliver stents do so through guiding catheters, it is understood that the decision to do so in any individual case will depend on the vascular anatomy, lesion pathology, and the experience of the individual operator. A guiding catheter or introducer sheath, which is compatible with the stent delivery system dimensions, will be used to establish vascular access. When possible, the guiding catheter should be positioned proximal to the target artery with a matching co-axial internal dilator. All CREST sanctioned variations in regard to guiding catheter use are specified in the Manual of Operations (MOP).

Prior to stent implantation, biplanar bilateral carotid cerebral angiography is employed to characterize intraluminal filling defects, estimate target lesion stenosis, and determine target artery diameter.

The decision to pre-dilate the carotid lesion prior to stent deployment is recognized to reflect a variety of factors related to device and lesion characteristics. The decision whether or not to use pre-dilatation, therefore, resides with the individual operator in any individual case. If a pre-dilatation strategy is chosen, the Investigator should pre-dilate with an appropriate size balloon dilatation catheter to insure that the inflated diameter is 0.6-1.0 times the true lumen diameter. Additionally, pre-dilatation should provide a minimum opening of 2.5 mm. If a no pre-dilatation strategy is chosen, there must be a minimal luminal opening of 2.5 mm to enable passage of the stent delivery system.

3.1.3 EMBOLIC PROTECTION DEVICE - OPERATOR GUIDELINES

The ACCUNET Systems should be utilized in all patients undergoing CAS in CREST, except when there is an issue of technical feasibility or in situations where the Investigator feels that the potential risks of employing an Embolic Protection Device (EPD) outweigh its advantages. Refer to the EPD manufacturer's product labeling for information concerning Precautions, Warnings and detailed instructions for EPD delivery and deployment.

Specific anatomic inclusion criteria for the EPD are as follows:

1. Expected ability to deliver the EPD distal to the lesion (absence of excessive tortuosity) and an available straight or mildly angulated segment ≥ 4 cm in the distal ICA (prior to the petrous portion of the vessel) in which to place the embolic protection device.
2. The diameter of the straight or mildly angulated segment, in the distal ICA prior to the petrous portion of the vessel, must be visually estimated to be ≥ 3.25 mm and ≤ 7.5 mm.

Examples of contraindications to the use of an EPD include, but may not be limited to:

- Extreme ICA tortuosity.
- Tortuosity immediately distal to a high-grade stenosis.
- If the distal filter is positioned and there is any concern for distal ICA spasm or intimal injury.
- An inability to safely cross the lesion with the EPD. Examples:
  - extremely tight and/or long stenosis;
  - sharp angulation at the origin of the internal carotid artery;
  - distal cervical carotid anatomy which precludes safe or effective placement of the embolic device;
  - distal cervical carotid arterial diameter too small or too large for the EPD.

- Situations where, in the operators' judgment, it is unsafe to place the EPD at the beginning of the procedure, but where it is felt safe to place the device after pre-dilatation of the carotid stenosis.

3.1.4 CAROTID STENT SYSTEM – OPERATOR GUIDELINES

The appropriate size stent shall be selected after review of the patient's baseline angiogram for determination of the reference vessel diameter. The diameter and length of the stent should be chosen according to the recommendations of the stent manufacturer as specified in the device labeling.

Prior to use, the carotid stent system will be inspected and prepared according to the Instructions for Use (IFU). Refer to the carotid stent system manufacturer's product labeling for information concerning Precautions, Warnings and detailed instructions for stent delivery and deployment.

If a guiding catheter is employed to assist in stent deployment, it should be positioned as close as possible to the target segment, without creating an impediment to stent expansion. Confirmation of satisfactory stent positioning prior to stent deployment is accomplished by contrast injection in the target vessel through the guiding catheter. Occasionally, it may be possible to accurately position the stent within the target vessel segment without the need for contrast injections, by noting its fluoroscopic relationship to radiopaque landmarks, most notably calcification present within the target plaque.

In certain cases it may not be feasible or even desirable to attempt to cover the entire diseased segment by means of a single stent. Vascular tortuosity may preclude optimal stent coverage by one device. If adequate coverage by one stent be impossible, a second stent may be used. The second stent should have the same internal diameter (ID) as the first stent deployed. The shortest stent length consistent with total lesion coverage is mandated. If a tapered stent is used and a second stent is necessary, the second stent should match the ID of the adjacent tapered stent.

Post-dilatation of the stent is recommended to closely approximate the stent to the vessel wall. If the result is technically unsatisfactory (greater than a 30% residual stenosis or approximation of the external surface of the stent to vessel wall is incomplete), post-dilatation should be performed. Incomplete approximation is defined as contrast on angiography, or echolucency on ultrasound, visualized between the artery wall and the stent struts. If incomplete approximation of the stent to the arterial wall is documented, post-dilatation at low pressure using a balloon not to exceed 1.2 times the estimated diameter of the target segment is performed. Repeat biplane angiography should be performed after the final inflation. The cranial-caudal angulation and obliquity must be the same as those used to determine the pre-treatment target stenosis.

3.1.5 CRITERIA FOR BAILOUT OR ALTERNATIVE PROCEDURES

Surgical rescue by means of arteriotomy or endarterectomy may be indicated for complications not responding to endovascular corrective measures, including:

1. Hemodynamically significant flow-limiting (TIMI grade 0 or 1) dissections or intraluminal filling defects in the target arterial segment.

2. Uncorrectable stent deformation encroaching on the arterial lumen.
3. Arterial rupture.

Patients should not be pre-treated with thrombolytic agents prior to starting the intervention. Intravenous or intra-arterial thrombolytic therapy may be used in symptomatic cases of thrombosis and thromboembolism complicating CAS. Operators may use intravenous thrombolytics to treat symptomatic cerebral emboli, that:

1. Occur during CAS, and
2. Occlusions including vessels up to third order branches of the middle cerebral and/or anterior cerebral arteries.

If there is an asymptomatic filling defect post-procedure the following steps should be followed for patient management:

1. If, after the final inflation, there is an asymptomatic intraluminal filling defect at the target site with flow ≤ TIMI grade 2, use a heparin infusion to maintain the PTT 2.0 to 2.5 times the control PTT, and repeat angiography at 24 hours ± 4 hours.
2. If the TIMI grade is > 2 at the time of the repeat angiogram, stop the heparin.
3. If the TIMI grade is ≤ 2 at the time of the repeat angiogram, convert the patient to Coumadin and maintain INR between 2.0 to 2.5 for 3 weeks.

Transfer the patient to an intensive care unit for a minimum of 12 hours.

3.1.6 CONCOMITANT MEDICAL THERAPY

Forty-eight hours before the procedure, all CAS patients (lead-in and RCT) should receive the following medications:

- Aspirin 325 mg b.i.d. (soluble)
- Clopidogrel 75 mg b.i.d. (minimum of 4 doses)

If the patient is unable to tolerate Clopidogrel, Ticlopidine may be substituted:

- Ticlopidine 250 mg b.i.d. (minimum of 4 doses)

The requirement of this 48 hour pre-procedure twice a day regimen will be satisfied for those patients who are already on the Aspirin/Clopidogrel regimen (minimum Aspirin 81 mg b.i.d., Clopidogrel 75 mg b.i.d). Patients taking other aspirin containing medications (e.g., dipyridamole/aspirin, i.e., Aggrenox) that do not include the minimum dose of aspirin must be able to tolerate a change to the protocol prescribed pre-procedure medication regimen to qualify for participation. For those patients in whom pre-treatment with the outlined antiplatelet regimen 48 hours pre-procedure is not possible, the following medication regimen may be utilized a minimum of 4 hours prior to the procedure.

- Aspirin 325 mg x 2 tablets
- Clopidogrel 75 mg x 6 tablets

Post procedure, all CAS patients (lead-in and RCT) should receive soluble aspirin 325 mg 1 to 2 tablets p.o. daily for 30 days, then 1 tablet p.o. daily thereafter (Note: 81 mg may be used if patient can not tolerate the higher aspirin dose). For the first 4 weeks post-procedure, all CAS patients should also receive either clopidogrel 75 mg 1 tablet p.o. daily or ticlopidine 250 mg 1 to 2 tablets p.o. daily. After the first four weeks the duration of the ticlopidine or clopidogrel will be per current recommendation of the manufacturer and/or standard practice. If ticlopidine is prescribed, it must be administered with the appropriate safety monitoring at two weeks and at one month. After the first four weeks, either Aggrenox (200 mg dipyridamole/ 25 mg aspirin) b.i.d or clopidogrel may be substituted for aspirin.

Antiplatelet and anticoagulant therapy is summarized as follows:

All Carotid Stent Patients				
Medication	**Pre-Procedure**	**Intra-Procedure**	**Post-Procedure**	**Post-Discharge**
Heparin[1]	PRN	Maintain ACT 250-300 sec. [1]	PRN[2]	None
Aspirin	325 mg p.o. b.i.d[2] (Begin 48 hours before)	None	325 mg [3] 1 to 2 tablets p.o. daily for 30 days	325 mg [3,4] 1 tablet p.o. daily thereafter
Clopidogrel	75 mg p.o. b.i.d. daily (Begin 48 hours before)	None	75 mg 1 tablet p.o. daily for 4 weeks	---
Ticlopidine (instead of Clopidogrel)	250 mg p.o. b.i.d. (Begin 48 hours before)	None	250 mg 1 to 2 tablets p.o. daily for 4 weeks	---

[1] Bivalirudin may be substituted for heparin. Use in accordance with manufacturer's instructions. ACT's are not collected when bivalirudin is used as the procedural anticoagulant.
[2]Heparin may be given post-procedure as needed
[3]May be substituted with 81 mg tablet if patient can not tolerate 325 mg dosage.
[4] After four weeks may be substituted with Aggrenox b.i.d. or clopidogrel.

Patients who are intolerant to a combination of Aspirin and Clopidogrel or Aspirin and Ticlopidine are ineligible for CREST participation. It is recommended that when possible, antihypertensive agents should be taken with a sip of water on the morning prior to procedure.

3.1.7 POST-CAS PATIENT MANAGEMENT

Sheath Removal and Ambulation

Remove the introducer sheath from the arterial access site when the ACT is <150 seconds. Approved vascular closure devices are allowed providing the device is used according to the manufacturer's IFU, the operator has been properly certified in the device being used, and has completed at least 20 procedures with the size of device to be used prior to using devices enrolled in the trial. If a vascular closure device is used, the above stated ACT parameter does not apply. However, the last ACT prior to closure of the puncture site will be recorded on the appropriate case report form (CRF).

3.2 CEA

For patients randomized to the CEA treatment arm, the CEA is to be performed by a CREST-certified surgeon. The surgeon responsible for the specific operation must have been reviewed and approved by the CREST SMC. The individual must be the primary operator in the procedure. Under no circumstances is the responsibility for conduct of the operation delegated to a surgeon who is not approved by the applicable study committee.

3.2.1 REQUIREMENTS FOR CERTIFICATION

See Sections 11.3.2.

3.2.2 GUIDELINES FOR CEA

Details of the guidelines for endarterectomy are provided in the MOP. Like ACAS and NASCET, minimal guidelines are provided for the conduct of the procedure, and surgeons are provided the freedom to perform the procedure in the manner that has resulted in the low morbidity and mortality required for their participation.[8,10]

Aspects of the management of the patient during and after operation are not dictated by CREST, but the techniques and methods used will be documented on the appropriate forms. The technique of CEA will not be dictated in the study since use of patches, shunts, or intraoperative monitoring is variable dependent upon the individual surgeon's practice. However, intraoperative details such as type of anesthetic, use of shunt, patch or monitoring will be recorded.

3.2.3 CONCOMITANT MEDICAL THERAPY FOR CEA PATIENTS

Forty-eight hours before the procedure, all patients should receive antiplatelet therapy consisting of aspirin 325 mg p.o. daily. These patients should remain on aspirin 325 mg daily indefinitely (at least one year). For those patients intolerant at this dose, acceptable alternatives include ticlopidine 250 mg b.i.d., clopidogrel 75 mg p.o.q.d., aspirin 81 mg p.o. daily, or Aggrenox b.i.d.

3.3 CLINICAL AND LABORATORY TESTS

Summary of Required Testing – Lead-In Patients				
Test	**Pre-Procedure**	**Post-Procedure**	**Post-Discharge 1 Month**	**Post-Discharge 12 Months**
Carotid duplex ultrasound		√[1]		√
CT scan/MRI	√[2]		PRN[2]	PRN[2]
TIA/Stroke Questionnaire	√		√	
Neurological exam	√[3]	√[3,8]	√[3]	√[3]
NIH Stroke Scale (NIHSS)	√[3]	√[3,8]	√[3,7]	√[3,7]
Modified Rankin Scale	√[3]			
Barthel Index	√[3]			

Medical Hx, Risk Factor Profile	√			√
ECG	√	√[4]		
Cardiac Enzymes (CPK, CK-MB or troponin)	√	√[5]		
Lipid Profile	√			
SMAC-7	√			
Fasting Blood Sugar	√			
Cerebral Angiogram	√[6]		PRN	PRN

[1]May be performed between 1 and 30 days post-procedure, exams are to be forwarded to the Core Lab regardless of whether performed by a CREST credentialed laboratory or not.

[2]Most recent pre-procedural neurological image will be used for baseline (if available), and additional CT scans should be performed as needed to evaluate subsequent cerebrovascular events.

[3]Neurological examination will be performed by the study neurologist or independent neuroscientist/ physician certified in the use of NIHSS. This physician cannot be the one that performed the study procedure on the patient.

[4]In addition to ECG 6-48 hours post procedure, an ECG should be obtained for chest pain lasting >15 minutes or for symptoms indicating myocardial ischemia.

[5]In addition to cardiac enzymes (CPK and CK-MB or troponin) 6-8 hours post-procedure, cardiac enzymes q 8 hr x 3 with pathological elevation of post-procedural enzymes, for ECG changes, or chest pain lasting >15 minutes.

[6]May have been performed prior to enrollment to qualify % stenosis and again as part of the procedure.

[7]NIHSS must be performed 3 months after the occurrence of a potential stroke endpoint.

[8]Performed between 18-54 hours post-procedure by the study neurologist or independent neuroscientist/ physician.

Summary of Required Testing – Randomized Patients			
Test	**Pre-Procedure**	**Post-Procedure**	**Post-Discharge**
Carotid duplex ultrasound	√[8]		1,6,12 months[1]
CT scan/MRI	√[2]		PRN[2]
TIA/Stroke Questionnaire	√	√[10]	1,3, then every 3 months[3]
Neurological exam	√[4]	√[4, 10]	1, 12 months[4]
NIH Stroke Scale (NIHSS)	√[4]	√[4]	1,6 months[4,5,9,11]
Modified Rankin Scale	√		1,6 months[5]
Barthel Index	√		1,6 months[5]
Quality of Life Scales	√		2 weeks,1 month, and 1 year
Medical Hx, Risk Factor Profile	√		1,3, then every 3 months

Summary of Required Testing – Randomized Patients			
Test	**Pre-Procedure**	**Post-Procedure**	**Post-Discharge**
ECG	√	√[6]	1 month[6]
Cardiac Enzymes (CPK, CK-MB or troponin)	√	√[7]	
Lipid Profile	√		6,12 months[1]
SMAC-7	√		6,12 months[1]
Fasting Blood Sugar	√		6,12 months[1]
Cerebral Angiogram	√[8]		PRN

[1]After 12 months, testing performed every twelve months until study is completed.

[2]Most recent pre-procedural neurological image will be used for baseline (if available), and additional CT scans should be performed as needed to evaluate subsequent cerebrovascular events.

[3]Testing performed every three months at clinic visit or via telephone until study is complete.

[4]Neurological examinations performed pre-procedure, immediately post-procedure and at the 1 and 12 month follow-up visitswill be performed by the study neurologist or independent neuroscientist-physician certified in the use of NIHSS. This physician cannot be the one that performed the study procedure on the patient.

[5]Testing performed every six months until study is complete.

[6]In addition to post-procedural ECG, an ECG should be obtained for chest pain lasting >15 minutes or for symptoms indicating myocardial ischemia.

[7]In addition to post-procedural cardiac enzymes (CPK and CK-MB or troponin), cardiac enzymes q 8 hr x 3 with pathological elevation of post-procedural enzymes, for ECG changes, or chest pain lasting >15 minutes.

[8]Cerebral angiogram or ultrasound must be performed pre-randomization, pre-procedure to qualify patient on % stenosis. Most recent pre-procedural carotid duplex ultrasound is required. Additionally, if pre-procedural ultrasound shows < 70%, a pre-procedural angiogram, CTA or MRA are required. See section 2.2.3 for more details. An angiogram will also be performed as part of the procedure on patients randomized to CAS.

[9]NIHSS must be performed 3 months after the occurrence of a potential stroke endpoint.

[10]Performed 18-54 hours post-procedure by the study neurologist or independent neuroscientist/ physician.

[11]At the 6 month follow-up visit and visits beyond 1 year, the NIHSS may be administered by a health care professional within the study staff that is certified in the use of the NIHSS should the study neurologist/neuroscientist be unavailable.

3.3.1 Examination Components

Pre/Intra Procedure

Lead-in Participants

The following should be performed within one year prior to enrollment in the lead-in phase to determine eligiblity:

- Cerebral angiogram. The angiogram can be performed on the day of procedure. If the angiogram performed on the day of procedure indicates the patient is not

eligible, the patient is not enrolled; however, if an adverse event occurs during the angiogram, the patient is enrolled.

The following should be completed **within 180 days** prior to enrollment in the lead-in phase:

- Chemistry profile comprised of a lipid profile (HDL, triglycerides, and total cholesterol estimated LDL) and SMAC-7

The following should be completed **within two weeks** prior to enrollment in the lead-in phase:

- General history, risk factor profile and physical examination (H&P) prior to entering the study.
- Neurological examinations, NIH Stroke Scale, Modified Rankin Scale and Barthel Index performed by study neurologist or independent neuroscientist-physician.
- TIA/Stroke Questionnaire.
- ECG

The following should be completed **within 48 hours** prior to enrollment in the lead-in phase:

- Fasting blood sugar
- Cardiac enzymes: troponin, or CPK including CK-MB fractionation.

If available, the most recent pre-procedural neurological image must be documented in the case report form, and a copy of the image kept on file.

Randomized Participants

The following can be performed **within one year** prior to randomization:

- Cerebral angiogram. If the angiogram is greater than 60 days from date of potential randomization, then a carotid duplex ultrasound is required pre-randomization.

The following should be completed **within 180 days** prior to randomization or 2 weeks post-randomization (but pre-procedure):

- Chemistry profile comprised of a lipid profile (HDL, triglycerides, and total cholesterol estimated LDL) and SMAC-7.

The following should be completed **within 60 days** prior to randomization:

- Carotid duplex examination. If this examination is used to determine the degree of stenosis, then it must be performed at a vascular lab that has been certified by the CREST Carotid Duplex Ultrasound Core Lab.; if this scan shows <70%, then an angiogram or CTA/MRA is required.

The following should be completed **within two weeks** prior to randomization or 2 weeks post-randomization (but pre-procedure):

- General history, risk factor profile and physical examination (H&P) prior to entering the study.
- Neurological examinations, NIH Stroke Scale, Modified Rankin Scale and Barthel Index performed by study neurologist or independent neuroscientist-physician.
- TIA/Stroke Questionnaire.
- Quality of Life Assessment.
- ECG.

The following should be completed **within 48 hours** prior to randomization or 2 weeks post-randomization (but pre-procedure) in the RCT.

- Fasting blood sugar
- Cardiac enzymes: troponin, or CPK including CK-MB fractionation.

If available, the most recent pre-procedural neurological image must be documented in the case report form, and a copy of the image kept on file.

Caveat: Those tests and procedures that are required for confirmation that the patient meets all the inclusion criteria and does not have any of the exclusion criteria must be performed prior to randomization.

Post-Procedure/Pre-Discharge

Lead-in Patients

- Daily medical evaluation until time of discharge.
- Neurological examination performed by study Neurologist or independent neuroscientist-physician (18-54 hours post procedure).
- NIH Stroke Scale (NIHSS) 18 to 54 hours post procedure performed by study neurologist or independent neuroscientist-physician.
- ECG 6-48 hours post procedure.
- Cardiac enzymes: troponin or CPK including CK-MB fractionation at 6-8 hours.
- Carotid duplex ultrasound any time post-procedure from 1-day up to the 30-days.

Randomized Patients

- Brief history and physical examination daily while patient is in hospital.
- Neurological examination performed by study Neurologist or independent neuroscientist-physician (18-54 hours post procedure).
- TIA/Stroke Questionnaire 18 to 54 hours post procedure.
- NIH Stroke Scale (NIHSS) performed by study neurologist or independent neuroscientist-physician 18 to 54 hours post procedure.

- ECG 6-48 hours post procedure.
- Cardiac enzymes: troponin or CPK including CK-MB fractionation at 6-8 hours.

Note:

- For elevated cardiac enzymes, repeat test every eight hours until enzymes return to baseline.
- Obtain repeat ECG for chest pain lasting longer than 15 minutes or symptoms indicating myocardial ischemia.

Post-Discharge Follow-up

Lead-in Patients

- Physician visit with medical evaluation (history and physical examination) and neurological examination by study Neurologist or independent neuroscientist-physician will be performed at one-month and 12 months. *(Note: The TIA/Stroke Questionnaire will be administered at the one-month visit).*
- NIH Stroke Scale performed by study neurologist or independent neuroscientist-physician that is certified in the use of the NIH Stroke Scale. (Additionally, the NIH Stroke Scale must be obtained 3 months after the occurrence of a suspected stroke.)
- Carotid duplex examination will be performed in the early post-operative period (between 1 and 30 days post-procedure) and again at 12 months.

Note: If MI or stroke is suspected, definitions as outlined in 4.3.2 and 4.3.3 will be applied. Brain imaging with CT or MRI scan if clinically indicated in all patients for whom focal neurological symptoms or signs are reported.

Randomized Patients

- Blood tests: WBC with differential and platelet count at two and four weeks if patient is taking ticlopidine.
- ECG one month following procedure.
- Brief history and risk factor profile will be obtained every three months.
- Carotid duplex examinations will be performed at one-month, six months, 12 months, and at 12-month intervals thereafter.
- Neurological Examination by study Neurologist or independent neuroscientist-physician will be performed at one-month and 12 months.
- NIH Stroke Scale at one-month, six months, and every six-months thereafter. The Stroke Scales must be administered by a study neurologist or independent neuroscientist-physician at the one-month and 12 month visits; at the 6 month visit and visits beyond 1 year, the NIHSS can be administered by a health care professional within the study staff that is certified in the use of the NIH Stroke

Scale should the study neurologist/neuroscientist be unavailable. . (Additionally, the NIH Stroke Scale must be obtained 3 months after the occurrence of a stroke.)

- Modified Rankin Scale at one-month, six months, and every six-months thereafter.
- Barthel Index at one-month, six months, and every six-months thereafter.
- TIA/Stroke Questionnaire at each clinic visit and at each telephone contact. (One month, three months, and every three months thereafter until study exit.)
- Chemistry profile comprised of a lipid profile (HDL, triglycerides, and total cholesterol estimated LDL), fasting blood sugar, and SMAC-7 at six-months, 12 months, and at 12-month intervals thereafter.
- Quality of Life Assessment at baseline, 2 weeks, one month and at 1 year.
- CT scan or MRI post procedure as per standard of care for subsequent cerebrovascular events.

3.4 SUMMARY OF FOLLOW-UP PROCEDURES

Summary of Follow-up Procedures – Lead-In Patients	
Contact Period[1]	**Follow-up**
Post-Discharge (1 day to 30 days)	Carotid duplex ultrasound
One-month ± one week	***Physician office visit***: Medical history, risk factor profile, neurological examination, NIHSS, TIA/Stroke Questionnaire
12 months ± two weeks	***Physician office visit***: Medical history, risk factor profile, neurological examination, NIHSS, carotid duplex ultrasound

[1]This timeframe is the *targeted window* when contacts should be scheduled. There is an *acceptable window* when data will be accepted for a contact scheduled during that time frame. For the 1 month contact the acceptable window is -one week/+ two weeks; for all other contact points the acceptable window is +/- 6 weeks. If a visit does not occur within these timeframes, then it is coded as a missed visit. Time windows are determined based on the date of procedure for lead-in patients.

Summary of Follow-up Procedures – Randomized Patients	
Contact Period [1]	**Follow-up**
Two weeks	***Blood tests***: If required for prescribed medications ***Telephone contact:*** QOL questionnaire by core lab designee
One-month ± one week	***Physician office visit***: Medical history, risk factor profile, neurological examination, NIHSS, TIA/Stroke Questionnaire, Modified Rankin Scale, Barthel Index, carotid duplex ultrasound, ECG, Quality of Life Scales
Three months ± two weeks	***Telephone contact:*** Medical history, risk factor profile, TIA/Stroke Questionnaire
Six-months ± two weeks	***Physician office visit:*** Medical history, risk factor profile, , NIHSS, Modified Rankin Scale, Barthel Index, TIA/Stroke Questionnaire, carotid duplex ultrasound, lipid profile, fasting blood sugar, and SMAC-7

Summary of Follow-up Procedures – Randomized Patients	
Nine months ± two weeks	***Telephone contact:*** Medical history, risk factor profile, TIA/Stroke Questionnaire
12 months ± two weeks (+ annually until study exit)	***Physician office visit***: Medical history, risk factor profile, neurological examination (note: a neurological examination other than the stroke scales are not performed after the first annual follow-up) NIHSS, TIA/Stroke Questionnaire, Modified Rankin Scale, Barthel Index, carotid duplex ultrasound, Quality of Life Scales (note: quality of life scales are not performed after the first annual follow-up), lipid profile and SMAC-7, fasting blood sugar
15 months ± two weeks (+ every 6 months until study exit)	***Telephone contact:*** medical history, risk factor profile, TIA/Stroke Questionnaire
18 months ± two weeks (+ annually until study exit)	***Physician office visit*****:** Medical history, risk factor profile, NIHSS, TIA/Stroke Questionnaire, Modified Rankin Scale, Barthel Index

[1]This timeframe is the *targeted window* when contacts should be scheduled. There is an *acceptable window* when data will be accepted for a contact scheduled during that time frame. For the 1 month contact the acceptable window is - one week/+ two weeks; for all other contact points the acceptable window is +/- 6 weeks. If a visit does not occur within these timeframes, then it is coded as a missed visit. Time windows are determined based on the date of procedure; if the procedure is not performed, then the time windows are determined from the date of randomization.

3.5 RISK FACTOR MANAGEMENT

The evidence accumulated to date supports attention to risk factor management in patients with atherosclerotic vascular disease, especially regarding cigarette smoking, antiplatelet therapy, blood pressure, blood lipids and lipoproteins, and diabetes.[71]

Thus, vascular disease risk factor management should be part of the routine medical care provided to patients who are enrolled in this trial. This care should be provided by the participants' primary physician. To insure the internal validity of the trial results, we are (on a yearly basis): (1) monitoring the prevalence and severity of the risk factors with the aim of assuring reasonable equivalence between the treatment arms, and (2) encouraging the local center to communicate directly with the patient's primary physician regarding the patient's risk factor levels and pertinent current recommendations for risk factor management.

3.6 QUALITY OF LIFE AND COST EFFECTIVENESS

Health-related quality of life (HRQOL) and functional status will be assessed using the Medical Outcomes Study 36-item health status questionnaire (SF-36) and Frenchay Activities Index (FAI) at baseline, one month following treatment, and at one year. In addition, all patients will be asked to complete the Health Utilities Index (HUI) at one year follow-up. These measures will be assessed using a standardized, written questionnaire at baseline, one month following treatment and at one year. In addition, the SF-36 and several disease-specific Likert scales will be administered 2 weeks after the

initial revascularization procedure by a trained interviewer from the quality of life coordinating center.

Medical resource utilization and cost data will be collected for the index hospitalization and throughout the follow-up period using standard Case Report Forms (CRFs). These CRFs will capture information regarding any subsequent hospitalizations, medical procedures, long-term care, and outpatient care required by each patient throughout the follow-up period. In addition, hospital summary bills (UB-92 forms) and detailed billing statements will be obtained for each patient's index hospitalization. These billing and resource utilization data will be converted into measures of medical care cost according to generally accepted methods that are outlined in *Appendix D*. At the completion of the study, the cost and quality of life data will be integrated into a computer-simulation model to perform a formal cost-effectiveness analysis (see *Appendix D*).

4.0 EFFICACY MEASURES

4.1 PRIMARY ENDPOINTS

The primary aim of CREST is to assess if the efficacy of CAS differs from that of CEA in preventing stroke, myocardial infarction and death during a 30-day peri-procedural period, or ipsilateral stroke over the follow-up period in patients with symptomatic (≥50%) or asymptomatic (≥60%) extracranial carotid stenosis. Data from CREST will be used to both provide an assessment of the differential efficacy of CEA and CAS, and also support a submission for a broadened indication for CAS for the subject device to regulatory agencies. Two separate analyses will be performed for this study. First, a traditional difference assessment for NIH submission, and second an equivalency analysis for submission to Regulatory Agencies.

The interventions considered in this proposal are performed to prevent ipsilateral stroke; however, there may be peri-procedural stroke (ipsi- or contra-lateral) and there may also be peri-procedural morbidity and mortality associated with the procedures.

For the NIH analysis, the null hypothesis is there is no difference in the event-free survival from stroke, MI and death during the first 30 days following the procedure, or ipsilateral stroke rate over a multi-year follow-up, between symptomatic patients with ≥ 50% carotid stenosis or asymptomatic patients with ≥ 60% carotid stenosis who are randomized to CAS versus CEA. The alternative hypothesis is that there is a difference in the event-free survival interval between the two treatments.

The primary endpoints are: (1) any stroke, myocardial infarction and death during the 30-day peri-procedural period, and (2) stroke ipsilateral to the procedure thereafter.

These primary endpoints are identical to those used for NASCET and ACAS except that myocardial infarction in the 30-day peri-procedural period has been added.

For the Regulatory Agencies analysis (to broaden device label), the null hypothesis is that the 1-year composite event rate (stroke, MI and death during the first 30 days following the procedure, and ipsilateral stroke rate between 31 days and 1 year) is greater for CAS

than for CEA. The alternative hypothesis is that the event rate is the same or lower for CAS than for CEA. (Equivalence is defined with a δ of 2.6%.)

The primary endpoints are: (1) any stroke, myocardial infarction and death during the 30-day peri-procedural period, and (2) stroke ipsilateral to the procedure between 31 days and 1 year.

For all endpoints, clinical documents relevant to the suspected endpoint (e.g., CT scan reports, ECGs, clinical notes, etc.) will be forwarded to the Clinical Events Committee (CEC) by the SAC after the documents have been masked for treatment group identity.

4.2 SECONDARY AIMS

The secondary NIH aims for CREST are to:

1. describe differential efficacy of CAS and CEA in male and female patients,
2. contrast peri-procedural (30-day) morbidity and post-procedural (after 30-days) morbidity and mortality,
3. estimate and contrast the morphology of the treated segment at 6 months and 1 year for the two procedures,
4. evaluate differences in measures of health related quality of life and cost effectiveness, and
5. identify subgroups of participants at differential risk for CAS and CEA.

The first (differential efficacy by gender), second (peri- and post-procedural treatment differences analyzed separately), and fifth (identification of groups at differential efficacy) of these secondary goals are closely related to the primary aim of the study. The outcome measures for these secondary goals are the same peri- and post-procedural events that are described above for the primary aim.

Secondary Regulatory Agency aims for CREST analyses include an assessment of:

1. One-year composite endpoint (similar to the primary endpoint) by strata defined by symptomatic status
2. Peri-procedural events (e.g. 30-day stroke, myocardial infarction, and death; stroke and death; major stroke and death)
3. Acute success
4. Target lesion revascularization at 12 months
5. Access site complication requiring treatment
6. Cranial nerve injury unresolved at 1 and 6 month

4.3 DEFINITIONS

4.3.1 DEATH

In the event of the death of a study patient, all possible efforts will be made to obtain relevant records from the hospital or the patient's primary care physician, including death certificates to determine the cause of death.

4.3.2 STROKE

Amaurosis fugax: Temporary (≤ 10 minutes) loss of vision in one eye due to insufficient flow of blood to the retina.

Transient Ischemic Attack (TIA): Temporary focal brain or retinal deficits caused by vascular disease that clear completely in less than 24 hours.

Non-Disabling Stroke is defined as an arterio-occlusive brain infarction characterized by the sudden onset of a neurologic deficit. The deficit must have persisted for a minimum of 24 hours. In all cases, patients must be non-disabled, i.e., Modified Rankin Score of ≤ 2.

Recurrent or New Ischemic Stroke is an acute neurological ischemic event of at least 24 hours duration with focal signs and symptoms. One or both of the following could be used as confirmatory evidence but not necessary for the designation of stroke: a one-point increase on the NIHSS or an appropriate new or extended abnormality seen on CT or MRI.

Stroke severity will be determined by the NIH Stroke Scale as of three months from the occurrence of the stroke. CT scans following a suspected event will be required and should be a minimum of 6 hours after the occurrence of an event to allow adequate detection and up to three months after the occurrence of an event, the interval between scheduled patient contact by clinic or phone visit.

Major Stroke: NIH Stroke Scale score of ≥ 9 at three-months.

Ipsilateral Stroke: Stroke affecting the cerebral hemisphere supplied by the study carotid artery.

The CEC will review and adjudicate all suspected strokes.

4.3.3 MYOCARDIAL INFARCTION

Diagnosis of myocardial infarction (MI) will be based on clinical history of chest pain, electrocardiographic changes, and serum cardiac enzymes. A patient will be considered to have experienced an MI when there is confirmatory evidence of myocardial ischemia PLUS elevation of cardiac enzymes (CK-MB or troponin) to a value 2 or more times the individual clinical center's laboratory upper limit of normal**.**

Confirmatory evidence of myocardial ischemia includes any one of the following:

- Chest pain or equivalent symptoms consistent with myocardial ischemia,
- ECG evidence of ischemia including new ST segment depression or elevation > 1mm in 2 or more contiguous leads.

In addition MI will be classified as follows:

1. ECG criteria only: The presence of new pathologic Q waves in 2 or more contiguous leads that are present on the discharge ECG and not the baseline ECG or present on the 30-day ECG and not the baseline or discharge ECG.

2. Enzyme criteria only:
   - In the absence of interval coronary intervention or coronary artery bypass surgery, elevation of CKMB or troponin to 2 or more times the individual center's clinical laboratory upper limit of normal will be considered evidence of myocardial infarction by enzyme criteria only.
   - If coronary intervention is performed then CKMB or troponin > 3 times the individual center's clinical laboratory upper limit of normal will be considered evidence of myocardial infarction by enzyme criteria only.
   - If coronary artery bypass surgery is performed then CKMB or troponin > 5 times the individual center's clinical laboratory upper limit of normal will be considered evidence of myocardial infarction by enzyme criteria only.

Post-procedure ECGs of all participants enrolled in CREST will be classified for the presence of ECG evidence of MI based on a centralized reading. For those post-procedure ECGs reflecting MI the pre-procedural ECGs will also be evaluated centrally for the presence of the MI prior to procedure. Both the pre- and post-procedure ECGs will be classified as having an MI with a high or moderate likelihood, and will be analyzed for serial change to verify that the MI represents a new (incident) event. The Novacode modification[72,73] of the Minnesota Code[74] will be used for MI classification. These modifications were incorporated in the Novacode criteria on the basis of our experience from several multi-center clinical trials, in order to improve classification accuracy and stability.

The CEC will review and adjudicate all suspected MIs that occur within 30 days of the procedure.

4.3.4 ACUTE SUCCESS

CAS Arm

EPD System: Device delivered, deployed, and retrieved, as described in Appendix C.

Carotid Stent System: Device delivered, stent placed, and delivery system retrieved, as described in Section 3.1.3.

Procedure/Device Success: Attainment of final result, < 50% residual stenosis covering an area no longer than the original lesion, using the carotid stent system as described in Section 3.1.3.

Clinical Success: Procedure success without death, emergency endarterectomy, repeat PTA/thrombolysis of the target vessel, stroke, and MI within 30 days of the procedure.

CEA Arm

Procedure Success: Attainment of final result, patency of target vessel, without evidence of neurological complications at the end of surgery.

Clinical Success: Procedure success without death, emergency repeat endarterectomy of the target vessel, PTA/thrombolysis, stroke and MI within 30 days of the procedure.

4.3.5 CRANIAL NERVE PALSY

Cranial Nerve Palsy – Injury to cranial nerves in the vicinity of the treated carotid artery that has not resolved by one month and six months after the initial procedure. Symptoms will depend on the specific nerve that is injured, such as difficulty swallowing or paralysis of facial muscles.

4.3.6 VASCULAR/PROCEDURAL COMPLICATIONS

The evaluation of acute vascular complications, although not a primary endpoint, is important for any study of carotid intervention or surgery. All occurrences of vascular complications requiring treatment – hematoma, arteriovenous fistula, pseudoaneurysm, retroperitoneal bleed, peripheral or cranial nerve disorder, limb ischemia, access site or surgical incision infection will be documented.

4.3.7 BLEEDING COMPLICATIONS

Severe bleeding is defined as hemorrhage resulting in hemodynamic compromise or death. Moderate bleeding is defined as bleeding requiring transfusion or treatment, but without hemodynamic compromise. Bleeding complications requiring treatment will be documented.

5.0 ADVERSE EVENTS

There are three classifications for adverse events: adverse event, serious/severe adverse event, and unanticipated adverse device effect. Adverse event information will be collected throughout the study. Adverse events will be monitored until they are adequately resolved or explained.

5.1 DEFINITIONS

Adverse Event	An undesirable clinical occurrence in a subject whether it is considered to be device related or not.
Adverse Device Effect	An adverse event which was or may have been caused by a device.
Anticipated Adverse Event	Any undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a patient, whether or not considered related to the investigational product(s) or drug regimen prescribed as part of the protocol, predefined in the protocol and/or Instructions For Use (IFU), that

	is identified or worsens during a clinical study.
Serious/Severe Adverse Event	A study-related event that is fatal, life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, requires intervention to prevent permanent impairment/damage, results in persistent or significant disability, results in congenital anomaly, or results in cancer.
Unanticipated Adverse Device Effect	Any serious adverse effect on the health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the protocol and/or IFU or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of the patient.

5.2 ADVERSE EVENTS

The individual Investigator must decide when an adverse event has occurred. All serious and non-serious adverse events that occur within 30 days of the study procedure (and randomization if the procedure is deferred or not performed) must be recorded on the Adverse Event CRF and associated supplemental event forms as appropriate (e.g., Major Event Form, Neurological Event Form, Bleeding/Vascular Complications Form, etc.). An Adverse Event CRF is not required for events that occur after the 30 day period unless the event is: a neurologic event, a bleeding or cardiac event, carotid intervention, hospitalization associated with sequelae of stroke, device-related event, or unanticipated adverse device effect, or death.

Details for neurologic events, hospitalizations associated with sequelae of stroke, device-related events, unanticipated adverse device effects, bleeding and cardiac events, carotid interventions and deaths that occur within and after the 30 day period from the study procedure (and randomization if the procedure is deferred or not performed) will be documented on the Adverse Event CRF and associated supplemental event forms as appropriate (e.g., Major Event Form, Neurological Event Form, Bleeding/Vascular Complications Form, etc.).

All device-related (or procedure-related) adverse events or unanticipated adverse device (or procedure-related) events that occur at any time during follow-up are to be captured and reported as adverse events (whether serious or not).

A list of adverse events which may result from the use of the device or occur as a result of the procedure is described below.

Adverse events that may result from CAS include the following: arterial perforation, arterial rupture, arteriovenous fistula, bleeding complications, stent embolism, stent and/or vessel thrombosis, vessel occlusion, death, stroke, MI, dissection of the carotid

artery, carotid artery spasm, puncture site complications, hypotension, hypertension, pseudoaneurysm, groin arteriovenous fistula, contrast induced renal failure, restenosis of the stented segment, vascular complications which may require vessel repair, infection.

Adverse events that may be associated with the use of an EPD are: thrombosis of the filter, detachment and/or implantation of a component of the system, filter entanglement on the stent or other damage to the stent and mechanical failure of the device.

Adverse events that may result from CEA include the following: bleeding complications, vessel occlusion, dissection of the carotid artery, wound infection, respiratory insufficiency, cranial nerve injury (temporary and permanent), arterial rupture, hypotension, death, stroke, MI, wound hematoma.

5.3 SERIOUS/SEVERE ADVERSE EVENTS

Each adverse event or complication requiring reporting on an Adverse Event CRF (as described in Section 5.2 above) meeting the definition for serious/severe adverse event should be considered as such and reported immediately (within 24 hours) to the SDMC, regardless of presumed relationship to surgery or the investigational device(s). The Investigator or RC shall also report the event, if required, to the IRB/MEC.

Reports relating to the patient's subsequent medical course must be submitted to SDMC until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

Hospitalization or treatment for injuries or disease processes not related to the study procedure or vessel, although documented on the Clinic Visit or Telephone Contact CRF and/or Subsequent Hospitalization CRF, should not be treated as serious/severe adverse events. All hospitalizations that occur post randomization must be reported and categorized by type of event that triggered the hospitalization.

5.4 UNANTICIPATED ADVERSE DEVICE EFFECTS

When an adverse event meets the definition for unanticipated adverse device effect, or that relationship is unknown, the Investigator or RC shall report the event immediately to UMDNJ and the SDMC as soon as possible after the event has occurred. UMDNJ will be responsible for reporting unanticipated adverse device effects for the CAS arm and unanticipated adverse events for the CEA arm to Regulatory Agencies and the IRB/MECs.

6.0 EARLY WITHDRAWAL FROM THE STUDY

Following the introduction into the body of the intended device (for lead-in patients)or following randomization (for randomized patients), all living patients are encouraged to complete all follow-up visits, tests and telephone contacts. If the patient is unable or unwilling to complete clinic visits, protocol telephone visits may be substituted. Only those patients who have withdrawn consent post randomization will be exempt from follow-up, but will remain in the analysis.

7.0 STATISTICAL METHODS

7.1 STATISTICAL ANALYSIS AND POWER CALCULATIONS

This section summarizes the statistical analysis plans and power calculations, with complete details provided in *Appendix E*. Separate analyses will be performed to meet NIH and Regulatory Agency requirements.

The primary aim of CREST is to assess the differential efficacy of CAS versus CEA. The null hypothesis of this study is that no differences will be observed in the efficacy of CAS and CEA in the prevention of study endpoints over the follow-up period; in contrast to the alternative hypothesis that these two treatments will differ in efficacy.

The sample size of 2,500 subjects was selected to provide 90% power to detect absolute differences between treatment groups of 1.2% per year, with differences of less than 1.2% per year considered clinically insignificant.

7.2 DETERMINATION OF PRIMARY EFFICACY AND SAFETY

The primary endpoints for the NIH analysis are any stroke, myocardial infarction and death during the 30-day peri-procedural period, and stroke ipsilateral to the procedure afterward. The primary analysis for Regulatory Agencies is treatment differences in event rates (any stroke, myocardial infarction and death during the 30-day peri-procedural period, and stroke ipsilateral to the procedure between 31 days and 1 year). An intention-to-treat survival analysis will be used to assess this difference. Following the intention-to-treat principle, randomized patients who crossover, do not receive their assigned treatment, or withdraw for any reason (e.g., exclusion criterion discovered after randomization), will be analyzed with their assigned treatment group. The primary endpoint will be assessed using standard time event statistical modeling with adjustment for major baseline covariates including clinical center, age and stroke severity (TIA versus non-disabling stroke).

7.3 SECONDARY AIMS ANALYSES

7.3.1 NIH – SECONDARY AIMS

In addition to the primary NIH aim, CREST will address a number of secondary aims. Details of the anticipated secondary analyses are provided below:

1. A major secondary aim is to address the important and controversial issue of differential efficacy by gender. To assess the hypothesis that CAS versus CEA is differentially efficacious by gender, the interaction of treatment and gender will be estimated. The analysis approach to this secondary aim is a natural extension of the primary aim, and as such a proportional hazards approach to the assessment will be employed. A hazard ratio greater than 2.22 can be detected with 90% power.
2. Differences in the morphology of the treated segment will be assessed in both groups at 6 months and 1 year. The differences between groups will be assessed by analysis of the covariance with adjustment for velocities assessed at one-month post index procedure.
3. Because events during the peri-procedural period can be considered as a dichotomous outcome, differences in peri-procedural event rates will be assessed using logistic regression. The anticipated complication rate in the CEA arm of the study is 5.7% (based on a weighted average assuming final enrollment of 1400 symptomatic patients and 1100 asymptomatic patients), and there will be 90% power to detect differences between treatments if the CAS complication rate is below 3.2% or greater than 9.3%.
4. Differences in the post-procedural event rates will be assessed among those participants who are event free at the end of the peri-procedural period. Unlike the peri-procedural period, the outcome for the post-procedural period is "time-to-event" survival analysis. Differences between groups will be assessed using the proportional hazards model, and there will be 80% power to detect differences if the hazard ratio is less than 0.50 or greater than 2.00.
5. Differences in other (non-primary endpoint) major and minor complications will be assessed using logistic regression. Power to detect differences is a function of the incidence of specific complications; however, should a complication have approximately a 5% incidence, statistical power would be similar to that for peri-procedural events (see #2 above).
6. The identification of factors that may influence the relative efficacy of CAS and CEA is identical to the first secondary aim (establishing whether gender affects the differential efficacy). Gender has been selected for special attention because of evidence of a possible effect in previous studies; however, an identical testing approach will be employed to establish if other factors can play a role in differential efficacy. As for evaluating the effect of gender, the analysis approach for this aim is a proportional hazards analysis, and a hazard ratio greater than 2.20 can be detected with 90% power.

The analyses of the secondary aims associated with hypotheses associated with the health-related quality of life and cost will be conducted by a joint effort of the statisticians at HCRI and SDMC, with details described in *Appendix D*.

7.3.2 REGULATORY AGENCIES – SECONDARY AIMS AND ANALYSES

In addition to the primary aims for analysis for Regulatory Agencies, there are several secondary aims associated with the FDA submission, specifically assessment of:

1. One-year composite endpoint (similar to the primary endpoint) by strata defined by symptomatic status
2. Peri-procedural events (e.g. 30-day stroke, myocardial infarction, and death; stroke and death; major stroke and death)
3. Acute success
4. Target lesion revascularization at 12 months
5. Access site complication requiring treatment
6. Cranial nerve injury unresolved at 1 and 6 months

Additional secondary analyses that will be performed include:

1. "Poolability" of symptomatic and asymptomatic CAS and CEA patients in the assessment of the 1-year primary outcome measure.
2. Efficacy will be analyzed by evaluating long-term outcomes (beyond 1-year) using a composite measure of all stroke, death and MI within 30 days, plus ipsilateral stroke beyond 30 days. [Just an observation to remind others: this secondary analysis for regulatory is the primary analysis for the NIH)
3. Comparison of event rates, adjusted for baseline prognostic factors, in lead-in versus randomized CAS patients and lead-in CAS versus randomized CEA patients.
4. Additional analyses of the primary endpoint for the following sub-groups:
    a. "Recently asymptomatic" versus "always asymptomatic"
    b. Male versus female (i.e., gender interaction)
5. Evaluation of treated segment by ultrasound at 6 and 12 months

The approaches and power to detect differences is described for each of these secondary aims in Appendix E.

7.4 INTERIM ANALYSES

The CREST Investigators recommend two interim analyses, the first after approximately 500 patients have been accrued, and the second after approximately 1/2 of the patients have been accrued. Although all analyses will use the entire follow-up experience of the cohort (as for the primary aim), because there will not be an extensive follow-up experience at the first of these interim analyses, the primary motivation of this interim analysis is to address concerns associated with differences in peri-procedural event rates. By the time of the second interim analysis, the long-term follow-up experience will be growing, and this analysis offers the opportunity to stop the study early because of a potential large difference in the long-term outcome.

In order to maintain maximum power for the final analysis, and to simultaneously protect the overall alpha of the study, O'Brien-Fleming adjustments[75] will be made to the alpha for each of these tests. The statistical costs of this adjustment have been incorporated in the power calculations presented in *Appendix E*.

7.5 LEAD-IN PHASE ANALYSIS

As part of the lead-in/credentialing phase, CREST CAS operators will be required to perform approximately up to 20 stent implantations with the ACCULINK™ and ACCUNET™ Systems. These data will be evaluated by center, and reviewed by the IMC prior to center certification. Additionally, when analyzed in total, these data can be used to establish the risk of an "event" associated with the placement of a stent or EPD. While there is flexibility in the definition of "event" for the primary analysis of safety in the lead-in period, the same definition as the major CREST events – death, any stroke (regardless of hemisphere), or myocardial infarction within the first 30 days will be used. Complete Statistical Analysis and Power Calculations are in *Appendix E.*

8.0 DATA MANAGEMENT/MONITORING AND QUALITY CONTROL

8.1 REQUIRED DATA

All required data for this trial will be collected on standardized CRFs. (*Appendix G)*

8.2 RECORD COLLECTION

Hospital records for any re-admissions (admission note, discharge note, carotid duplex scan or carotid angiography, operative reports, and laboratory reports) must be collected to confirm clinical events. The standard procedural CRFs should be complete and ready for monitoring within 14 days of the procedure. All angiograms, carotid duplex ultrasounds, and ECGs should be sent to their respective core laboratories within two weeks of performance. Serious complications (death, MI, stroke, carotid artery occlusion, hemorrhage requiring transfusion, and other serious or life-threatening events) or device failures must be reported to SDMC within 24 hours. SDMC will immediately notify Dr. Robert Hobson at the CREST Administrative Center at UMDNJ upon initial notification of all unanticipated adverse device effects related to CAS and unanticipated adverse events related to CEA.

8.3 CLINICAL SITE TRAINING

The designated RC at each clinical site will be oriented to the study prior to beginning enrollment into the lead-in or randomization phase to become thoroughly familiar with the Protocol, CRFs, and with methods of data verification.

8.4 DATA MANAGEMENT

The SDMC is located at the University of Alabama at Birmingham, and employs a combination of clinical, analytical and information systems expertise in the coordination of large-scale, multi-center trials. UAB uses a decentralized data management system to assure data integrity and validity. Case report form data are entered on local databases and maintained in the local clinical centers. Transfer and synchronization of data between the local clinical centers and the central database at UAB is maintained through web connections, and is performed in the "background" at the clinical sites (does not require specific actions by the clinic staff). No patient identifiers will be contained in the central data-set. These data will be merged with the primary endpoint data that has been reported by the CEC.

8.4.1 DATA FROM CLINICAL SITES

All data for CREST will be collected on paper CRFs and entered on a local database in the clinical center. Data entry is expected within 14 days of enrollment or patient visits. Range and validity checks to ensure data quality are an integral part of the local database, as are systems to track outstanding queries. The original CRF will be retained in the clinical center. To track Core Laboratory data flow, the SDMC will provide the sites with Core Laboratory assessments status reports to provide support for clinic management identifying pending and overdue assessments.

8.4.2 DATA FROM THE CORE LABORATORIES

Data for CREST from the Core Laboratories can either be entered into local databases with support similar to that for the clinical centers (i.e., a distributed data management system) or original forms transferred to the SDMC for data entry (i.e., centralized data management system). Regardless, the original documentation will be maintained in Core laboratories. Both methods of transmittal will be tracked and entered into the central CREST database. For core laboratories transferring copies of data forms, the SDMC will perform data entry and validation on all paper data. The SDMC will provide each Core Laboratory blinded data tables for their review on a quarterly basis for quality control.

8.5 STUDY TIMELINE

Overall, the CREST project should complete recruitment by the summer of 2008, and each patient will be followed for an additional two years – implying the completion of the study by the summer of 2010. Each center will receive written approval designating approved Investigators. The recruitment goal is 2,500 patients. Patient follow-up will begin immediately after randomization as centers are phased in. The closure of data files and reporting of major study results will be completed within six months of the two-year follow-up of the last recruited patient.

9.0 STUDY ORGANIZATION

Investigators in CREST will be organized both by the organizational unit or center they represent and by their participation in the committee structure. The units participating in CREST are:

1. Clinical Centers
2. IDE Sponsor/Administrative Center
3. Statistical and Data Management Center
4. Central Angiographic Core Laboratory
5. ECG Central Reading Center
6. Central Ultrasound Core Laboratory
7. Economic Study and Quality of Life Research Center
8. Recruitment Center

While the Investigators will be supported from their organizational unit, the study will be governed by the committee structure.

9.1 EXECUTIVE COMMITTEE

The Executive Committee is the policy and decision-making committee for the study. The Committee provides clinical and scientific direction at the operational level and acts as the primary advisory body to the Principal Investigator, Dr. Robert W. Hobson, II. A major responsibility of this committee is monitoring and enhancing overall recruitment and by site, gender, and race, working with specific centers if deficiencies are found. The Executive Committee consists of the following:

1. Dr. Robert W. Hobson, II, PI, IDE Sponsor/Administrative Center
2. Dr. Thomas Brott, Co-Prinicpal Investigator, and Principal neurologist investigator
3. Co-PI, Statistical and Data Management Center
4. Co-PI, Interventional Radiologist
5. Co-PI, Interventional Cardiologist
6. Co-PI, Vascular Surgery
7. Co-PI, Neurosurgery
8. Angiographic and Duplex Ultrasound Core Laboratory Representatives
9. Canadian Representive
10. Quality of Life and Economics substudies
11. Ex-officio members

The Executive Committee will meet by conference call at least monthly to deal with interim business and to discuss the day-to-day and logistical needs of the study. Other individuals will participate in the activities of the Executive Committee, as needed, (e.g., representatives from the other Core Laboratories (Quality of Life/Economics Study Center, etc.) consultants, investigators from the participating centers, staff from the IDE Sponsor/Administrative Center, and SDMC.

9.2 STEERING COMMITTEE

The Steering Committee represents all of the clinical sites participating in the trial. The PI from each of the clinical centers and the Executive Committee will be represented on this committee. Various study design and planning committees within the Steering Committee assist the Executive Committee in such tasks as certification of stent operators and surgeons, site selection, writing, revising and implementing the MOPS, standardizing diagnostic or therapeutic methodology, monitoring and assistance with the recruitment of patients, and editorial work on abstracts, presentations and manuscripts. These committees, which report to the Executive Committee, include representatives from the IDE Sponsor/Administrative Center, and SDMC.

9.2.1 SURGICAL MANAGEMENT COMMITTEE

The SMC will review qualifying data submitted by potential participating surgeons and make recommendations to the Credentials and Site Selection Committees on the inclusion of qualified surgeons for the study. The Committee has established guidelines on minimal annual experience, as well as morbidity and mortality in the performance of carotid endarterectomy.

9.2.2 INTERVENTIONAL MANAGEMENT COMMITTEE

The IMC will review qualifying data submitted by potential participating interventionalists and make recommendations to the Credentials and Site Selection Committee on the inclusion of qualified operators for the study. The Committee has established guidelines on morbidity and mortality in the performance of CAS. This committee will determine training requirements for interventionalists and certify interventionalists prior to patient randomization.

9.2.3 MEDICAL MONITORING

Medical monitors will be identified by the Principal Investigator or designee. The medical monitor has responsibility for independent review and initial classification of major adverse events and potential major events including stroke, myocardial infarction, death, TIA, procedural complications that occur within 30 days of the procedure or randomization (with the exception of hypertension and hypotension which did not prolong hospitalization), embolic protection device or stent failure, repeat intervention, acute and sub acute stent occlusion, bleeding complications and any adverse event documented on the "Major Event" case report form such as major complications related to the trial medication (leucopenia, thrombocytopenia, neutropenia). Medical monitoring will be performed on a frequent and ongoing basis.

9.2.4 CLINICAL EVENTS COMMITTEE

The CEC is made up of at least ten physicians (cardiologists, interventional radiologists, surgeons, and neurologists).

This committee has the responsibility for adjudication of whether a patient has reached a verified end point of stroke, myocardial infarction, and/or death. The CEC, in collaboration with the NIH grant authors (and approved by the CREST Executive Committee), will establish explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. The CEC is charged with the development of specific criteria used for the categorization of clinical events and clinical endpoints in CREST, within the framework of the definitions prespecified in this protocol. Such criteria will be reviewed and approved by the Data and Safety Monitoring Board (DSMB).

All members of the CEC will be blinded to the primary results of the trial. Committee members in the trial will not be allowed to classify subjects from his/her own site. The role of this committee is an ongoing one throughout the entire study period.

9.2.5 PUBLICATIONS AND PRESENTATIONS COMMITTEE

This committee will formulate publication policy for this collaborative research, and review all abstracts, papers, and scientific presentations utilizing study data. The Publications and Presentations Committee will be responsible for identifying topics for publication as well as making writing group assignments. The subcommittee will review and recommend approval or disapproval of all scientific abstracts and papers or presentations using unpublished study data, as well as every paper using published data that purports to represent official study views or policy.

Another major responsibility of this Committee is in the development of plans for the dissemination of trial findings and incorporation of the findings into medical care policy. This will involve not only reports in medical journals but consideration of continuing education courses, conferences and seminars and special efforts such as press conferences, editorials, physician newsletters and presentations at local medical association meetings.

9.2.6 EXTERNAL ADVISORY COMMITTEE

This committee is composed of senior scientists not contributing data to the study. This committee will be convened initially to review the final protocol and operations manual. Thereafter, these advisors will be called upon to review and discuss progress and problems relating to the trial and make recommendations for improvements. This committee will not have any confidential outcome data and is separate and distinct from the NIH-appointed DSMB.

9.3 DATA AND SAFETY MONITORING BOARD

A DSMB will be appointed by NIH staff to monitor the safety and efficacy of treatments. This committee will be independent of the Steering Committee and the study Investigators and will only report to the NIH. This committee will monitor the study

results for evidence of adverse or beneficial treatment effects throughout the study period.

10.0 CLINICAL CENTER RESPONSIBILITIES

10.1 INVESTIGATOR RESPONSIBILITY/PERFORMANCE

The designated PI at each site is responsible for the overall screening and enrolling of patients, as well as ensuring that all potential patients are considered for enrollment into CREST. The PI shall ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance with the highest standards of medical and clinical research practice. The PI will provide copies of the study protocol to all Co-investigators and other staff responsible for study conduct. In addition, the Trial PI, Robert W. Hobson, II M.D., at the CREST Administrative Center, UMDNJ-NJMS will administer the NIH grant in accordance with all applicable NIH guidance documents related to NIH supported multi-center clinical trials.

10.2 INFORMED CONSENT AND IRB/MEC APPROVAL

Each clinical center participating in this study will obtain IRB/MEC approval for the protocol and informed consent forms prior to patient enrollment. Until the study is completed, each Investigator will notify his/her IRB/MEC of the progress of this study, minimally, on an annual basis. Written approval must be obtained yearly to continue the study. Further, any amendments to the protocol, as well as associated consent form changes, will be submitted to the IRB/MEC and written approval obtained prior to implementation. The study will be explained to the patients in lay language. Patients will sign and receive a copy of an informed consent form prior to study participation. Patients will be assured that they may withdraw from the study at any time for any reason and receive alternative conventional therapy as indicated. Brochures, advertisements, posters, etc. may be used to educate patients and physicians about the study. Study Sponsor (UMDNJ) and the IRB/MEC approval of these materials will be obtained according to local and trial requirements.

10.3 SOURCE DOCUMENTATION

In compliance with national and international regulations, Investigators will maintain information in the study patient's medical records that corroborate data collected on the CRFs.

10.4 DEVICE ACCOUNTABILITY

The Investigator shall maintain adequate records of the receipt and disposition of the investigational devices, including date used. An Investigational Site Device Inventory Form supplied by UMDNJ will be used. When the investigation is discontinued, the Investigator shall return to the device manufacturer any unused study devices (stent or EPD) and the completed Ending Inventory Worksheet. The Investigator's copy of the Ending Inventory Worksheet must document the unused systems that have been returned.

Use of either of the Investigational Devices, the EPD or the carotid stent system, designated for the CREST study outside of the above-described protocol (i.e., compassionate use) is not allowed.

10.5 DATA TRANSMITTAL AND RECORD RETENTION

Required data will be recorded on the paper CRFs and subsequently entered on a decentralized data management system as soon as possible after the patient visit or contact or availability of test results. The CRFs and any supporting documents must be submitted to SDMC according to the outlined time windows.

All patient records, plus the Investigator's copy of the CRFs, device disposition records, and signed informed consent forms, must be kept by the Investigator for a minimum of two years after the applicable Pre-Market Approval (PMA) is approved, or until two years after investigation under the Investigational Device Exemption (IDE) has been discontinued and the Food and Drug Administration (FDA) has been notified, or as required by local regulation or law or institutional policy, NIH policy, whichever is longer.

10.6 NON-PROTOCOL RESEARCH

UMDNJ has a legal responsibility to report fully to regulatory authorities all the results of this sponsored clinical trial. No investigative procedures other than those in this protocol shall be undertaken on the enrolled patients without the agreement of the IRB/MEC and CREST Executive Committee.

11.0 REGULATORY REQUIREMENTS

11.1 GENERAL DUTIES (21 CFR 812.40 AND EN 540, 4.0)

As the IDE sponsor of this clinical trial, UMDNJ has the overall responsibility for assurance that the study meets the requirements of national and international regulatory agencies. UMDNJ will maintain compliance with the FDA Code of Federal Regulations, International Conference of Harmonization (ICH), Declaration of Helsinki and Good Clinical Practice Guidelines. The study design, MOPs preparation and determination of

the primary endpoints are the shared responsibility of the CREST Executive Committee, and SDMC. UMDNJ is responsible for obtaining and reviewing copies of IRB/MEC approvals prior to shipping the devices, selecting Investigators, ensuring proper investigative site monitoring and verification that appropriate patient informed consent is obtained. The Executive Committee of CREST will provide assistance to UMDNJ in performing these duties. Serious Adverse Event reports will be submitted as required by the IDE Sponsor, SDMC and IRB/MEC.

11.2 SELECTION OF INVESTIGATORS (21 CFR 812.43 AND EN 540, 5.4.1)

The combined CREST Credentials and Site Selection Committee, SMC and IMC, in collaboration with UMDNJ, will select qualified Investigators to perform procedures in this Trial. Devices will be shipped only to these approved Investigators. UMDNJ will obtain signed Investigator Agreements and the SDMC will provide the Clinical Centers with the information necessary to conduct the study.

11.3 SELECTION AND MONITORING OF CLINICAL SITES AND INVESTIGATORS

The primary concerns in clinical site selection for CREST are adequate experience with either CEA or CAS, commitment to safety, and consistency in adherence to the protocol. A substantial referral population (including female/minority representation) and an established stroke team are required for Trial participation.

11.3.1 SITE SELECTION

The Credentials and Site Selection Committee will review the credentials of those centers expressing interest and providing eligibility data. Criteria for judging the acceptability of centers include: (1) the presence of a sizable endarterectomy patient pool ($n \geq 50$ CEA/year/center), (2) special emphasis on representation by women ($\geq 40\%$) and minorities ($\geq 4\%$) in their endarterectomy pool to meet recruitment goals (approximately 18 patients/year/center), (3) experience in NIH clinical trials (one or more), (4) established low endarterectomy complication rates ($< 6\%$ for symptomatic disease) for individual surgeons - data to be submitted on no less than two participating surgeons, (5) the presence of an experienced interventional and surgical team (neurologists, vascular or neurosurgeon, interventionalist, nurse coordinator), (6) an established ultrasound laboratory which should be approved by the Intersocietal Commission on Accreditation of Vascular Laboratories (ICAVL), or American College of Radiology Certification, and (7) scientific/publication experience of the Investigators. Sites should qualify at least two surgeons and interventionalists. The goal among eligible centers is to objectively select the "best" centers for participation.

11.3.2 QUALIFICATION OF SURGEONS

Credentialing for surgeons who are candidates for participation in the CEA portion of the study has previously been evaluated and subsequently validated in the ACAS trial.[76] The SMC recommends that no fewer than 12 carotid endarterectomies be performed by each participating surgeon each year. In order to establish the frequency of operation as well as the individual surgeon's complication rate, a pre-study audit of each potential participating surgeon will be required. Each surgeon will be asked to submit his or her

last 50 cases or 12 months' consecutive experience (whichever is greater) with carotid endarterectomy. The information will include the date of operation, the date of discharge, the indication for operation, and whether or not a stroke or death occurred within 30 days of operation. Supporting documents will include a copy of the operative note and discharge summary. Each application will be reviewed by the SMC.

The SMC also recognizes that an audit of 50 cases, while practical, does represent a relatively small sample. The SDMC will inform the PI and SMC the first time a stroke or death occurs in a given institution. Under these circumstances, that institution will be placed on a watch status. Should a second death or stroke occur within that institution, this will trigger a potential audit of the institutional experience as well as the individual surgeon participation. This review may require a site visit and may result in dropping an individual surgeon or institution from participation in the trial. The nature of the audit will be determined by the SMC.

11.3.3 QUALIFICATION OF CAS OPERATORS

Since the use of CAS for carotid artery disease is relatively new, it is anticipated that there will be two classes of participating interventionalists; those who have had prior carotid stenting experience, and those who have had stenting experience in other vascular territories. Credentialing of the two groups by the IMC will be based upon different criteria, and therefore are described in separate sections.

Because carotid stenting and use of EPD does require specialized training, all operators without experience with these devices will be required to complete training. The Carotid Stent Operator Certification Program (CSOCP) is designed to flatten the carotid-stent learning curve without placing patients at risk. The program consists of intensive didactic and hands-on training focused on the prerequisites for use of EPD and carotid stenting.

Mandatory skills include techniques of carotid vascular access, balloon angioplasty, EPD use, as well as stent delivery and deployment. In addition to the aforementioned technical skills, carotid stent therapists must have expertise in cerebrovascular angiodiagnosis in order to identify and interpret findings related to co-morbid conditions and neurovascular complications, particularly those associated with iatrogenic cerebral atherothromboembolism.

Like the credentialing of surgeons, it is recognized that credentialing of interventionalists has similar limitations. For this reason, a similar continual monitoring of interventionalists will be conducted. The SDMC will notify the PI and the IMC whenever a stroke or death occurs in an individual institution. Upon notification, that institution will be placed on a "watch" status. A second event at the institution will trigger a potential audit. The nature of the audit will be determined by the IMC.

11.3.4 CREDENTIALING FOR INTERVENTIONALISTS WITH PRIOR CAS EXPERIENCE

In order to qualify for this category, the individual must have performed no fewer than 30 CAS procedures. Individuals who wish to be considered under this category will submit their entire carotid stent experience for up to 50 consecutive patients. Data will include

dates of admission and discharge, indication for procedure, and the 30-day peri-procedural stroke morbidity and mortality from any cause along with the procedural note and hospital discharge for each patient. Finally, follow-up information beyond 30 days with regard to patency and recurrent stenosis must be provided; and the mechanism for making this determination, either angiography or duplex scanning, must be documented. These candidates will be required to be trained on the use of both the EPD and the carotid stent system, which may include attending the Carotid Stent Operators Certification Program (CSOCP). However, prior to participation in the randomized study, they must perform up to approximately 20 CAS procedures at their institution (as designated by the CREST IMC). For these initial cases, the results will be reviewed by the IMC. If the number of events (stroke or death) is considered unacceptable, additional procedures may be required with appropriate proctoring prior to participating in the randomized study. For the purpose of training/proctoring a non-credentialed interventionalist, lead-in patients may be treated by an interventionalist that has received approval for the randomization phase of the program. These cases shall not detract from randomization of patients and should be limited to a maximum of 2 cases for each center randomization.

11.3.5 CREDENTIALING FOR INTERVENTIONALISTS WITH NO PRIOR CAS EXPERIENCE

This will be defined as those applicants who have fewer than 30 CAS procedures in their total experience. It is recognized that there will be applicants from four different specialty groups: (1) interventional cardiovascular radiology, (2) interventional neuroradiology, (3) interventional cardiology, and (4) vascular surgery. Entry qualifications for radiologists will be board certification as documented by a Certificate of Added Qualification in Vascular and Interventional Radiology. Equivalent certification by Neuroradiology, Cardiology, and Interventional Vascular Surgery is desirable.

For those individuals entering trial participation in this category, attendance and satisfactory completion of training which may include the CSOCP will be a prerequisite to participation. Those individuals, by appropriate qualification and successful completion of the training, will be certified to begin carotid stenting. However, prior to participation in the randomized study, they must perform up to approximately 20 CAS procedures at their institution (as designated by the CREST IMC). For these initial cases, the results will be reviewed by the IMC. If the number of events (stroke or death) is considered unacceptable, additional procedures may be required with appropriate proctoring prior to participating in the randomized study. For the purpose of training/proctoring a non-credentialed interventionalist, lead-in patients may be treated by an interventionalist that has received approval for the randomization phase of the program. These cases shall not detract from randomization of patients and should be limited to a maximum of 2 cases for each center randomization.

11.4 MONITORING (21 CFR 812.46 AND EN 540, 5.5)

UMDNJ or its designees will conduct monitoring at Clinical Centers to ensure that all Investigators are in compliance with the protocol and the Investigator's Agreement. UMDNJ will evaluate and report to the CREST Executive Committee circumstances where an Investigator deviates from the clinical protocol and corrective action will be taken as necessary.

UMDNJ will review significant new information on the CAS procedure, including unanticipated adverse events and ensure that such information is provided to reviewing IRBs/MECs and to the device manufacturer. This information will be provided to the FDA, NINDS, other regulatory authorities, and Investigators worldwide in accordance with applicable regulations.

SDMC will review significant new information on the CEA procedure, including unanticipated adverse events and ensure that such information is provided to reviewing IRBs/MECs. This information will be provided to the UMDNJ, FDA, NINDS, other regulatory authorities, and Investigators worldwide in accordance with applicable regulations.

11.5 SUPPLEMENTAL APPLICATIONS (21 CFR 812.35 (A) AND (B) AND EN 540, 5.6.14 AND 5.6.17)

As appropriate, UMDNJ will submit changes to the investigational plan to the FDA/Regulatory Agency and Investigators to obtain IRB/MEC re-approval.

11.6 FINANCIAL DISCLOSURE (21 CFR 812.110)

All Investigators are required to provide the study sponsor with documentation of individual financial interest related to the device manufacturer or UMDNJ. Participating Investigators will complete a Financial Disclosure Form and submit to the sponsor at the start of the Trial and on a yearly basis for the duration of the Trial.

11.7 SUBMITTING REPORTS (21 CFR 812.150 AND EN 540, 5.4.12 AND 5.6.15)

UMDNJ will submit the appropriate reports identified in this section of the regulation. This includes unanticipated adverse device effects, withdrawal of IRB/MEC approval FDA/Regulatory Agency approval, annual progress reports, recall information, final reports and device use without informed consent.

11.8 MAINTAINING RECORDS (21 CFR 812.140 AND EN 540, 5.4.3)

The SDMC will collect and maintain data from case report forms and adverse event adjudication data. UMDNJ will maintain correspondence, shipment of devices, adverse device effects and other regulatory records related to the clinical trial. In addition, the local centers, SDMC, Core Laboratories, CREST Committees, the UMDNJ and clinical sites will maintain study records for two years after PMA is obtained, or two years after the FDA/Regulatory Agency is notified that research under the IDE has been terminated, by UMDNJ or as required by local regulation, NIH policy, or law (whichever is longer). Record retention dates will be provided by UMDNJ to all concerned.

11.9 INFORMED CONSENT (21 CFR PART 50 AND EN 540, 5.6.9) AND HUMAN

SUBJECTS COMMITTEE (21 CFR PART 56 AND EN 540 5.6.13)

All patients must provide written informed consent in accordance with each clinical site's Human Subjects Committee (IRB/MEC). A copy of the consent form from each center must be forwarded to UMDNJ for regulatory review and approval prior to implementation. Approvals for continuation of the study at each clinical site must be obtained according to their local IRB/MEC requirements (at a minimum, annually) and forwarded to UMDNJ.

12.0 USE OF HUMAN SUBJECTS/ETHICAL CONSIDERATIONS

12.1 RECRUITMENT AND CONSENT PROCEDURES

Patients are recruited from:

1. Hospitalized and ambulatory stroke and TIA patients and screened to confirm that a non-disabling stroke or TIA has occurred and that the patient has ≥ 50% stenosis by angiogram or ≥70% by duplex ultrasound, or
2. Asymptomatic patients with documented stenosis ≥ 60% by angiography or ≥ 70% by duplex ultrasound.

After identification of a patient meeting these minimum eligibility criteria, the patient's physician is contacted by the local PI or co-investigator for permission to contact the patient about the study. Prior to collecting study data, the details of the study will be explained in detail to the participant including: (1) that the study represents a research effort, (2) that participation is voluntary, and there is no penalty for withdrawal, (3) any anticipated costs to the patient for participation, (4) potential risks and benefits for participation, and (5) contact information for additional concerns. Patients are informed of the purpose of the study, the treatment alternative, the random manner of assignment to treatment, the need to be available for telephone follow-up and return clinic visits at regular intervals for questionnaires and/or medical tests, and of their options to accept or refuse entry into the study. Only with the full and complete understanding of the study, and signed informed consent, should the evaluation of the potential participant continue.

12.2 POTENTIAL RISKS TO PATIENTS (CAS)

EPD: Risks that may be associated with the EPD are: thrombosis of the filter, filter entanglement on the stent or other damage to the stent and mechanical failure of the device.

Carotid Stent System: Stents are metallic foreign bodies, which remain in the artery indefinitely. Complications that may be associated with stenting include thrombosis, stent migration, arterial rupture, embolization, and stent deformability; preliminary evidence suggests that the incidence of these complications after carotid stenting is low. In addition, there may be a potential for stents to impact the feasibility of imaging and surgical procedures.

Stent thrombosis is a complication that is well described in the coronary and peripheral interventional literature. Several causes of stent thrombosis have been documented and

there are effective strategies for minimizing this complication. Stent delivery by the operator to the target site is an important determinant of thrombosis. Proper apposition of the stent to the arterial wall with minimal residual narrowing reduces the risk of thrombosis. Treatment with aspirin and clopidogrel or ticlopidine also reduces the incidence of stent thrombosis. As a result, thrombosis is distinctly uncommon with proper operator technique and use of antiplatelet medication.

Stent migration may occur but is uncommon. Endovascular snares have been developed to deal with this problem. In the majority of cases, experienced operators retrieve stents that have migrated, without permanent complications. Arterial rupture is distinctly uncommon. Proper device selection as well as the choice of inflation pressure effectively minimizes this complication.

Symptomatic embolization secondary to carotid stenting appears to be rare. Asymptomatic embolization has been documented with transcranial Doppler. Its significance is uncertain. However, the same phenomenon has been documented during carotid endarterectomy.

Stent deformation (crushing) that reduces the cross sectional area of the stents lumen is rare. It has been described with only one manufacturer's stent. Some of the newer stents, for example Nitinol stents, are specifically designed to prevent this problem.

Current stents can potentially produce artifacts on MRI imaging. If MRI artifacts occur, other scanning modalities can be used; e.g., CT scanning. Although stents are metallic, they do not appear to be affected, in a clinically important way, by the magnetic field associated with MRI. Empirically, they do not migrate when placed in a MRI scanner and several patients with stents in the cerebral circulation have undergone MRI without discernible consequences.

12.3 POTENTIAL RISKS TO PATIENTS (CEA)

Carotid endarterectomy has been used for decades and hundreds of thousands of CEAs have been performed in this country. Consequently, there is a large pool of highly skilled surgeons. Only experienced surgeons who have competence in carotid endarterectomy have been invited to participate in CREST. In addition, they are required to demonstrate their continued competence in endarterectomy prior to the randomized phase of CREST.

Risks associated with CEA are well characterized in individual center and cooperative study reports. In symptomatic patients, 30-day risk of stroke and death should not exceed 5-7%, while in asymptomatic patients, the 30-day risk of stroke or death should not exceed approximately 3-5%. These data were utilized by the SMC in selecting CREST clinical sites. Other risks include cranial nerve palsies, usually transient, the infrequent myocardial infarction (<1%), and wound hematoma or infection, generally less than 3-5%.

12.4 PROTECTING AGAINST POTENTIAL RISKS TO PATIENTS

CAS is a relatively new procedure. However, the use of arterial stents in other arteries is common. Consequently, many operators are available with considerable experience in coronary and peripheral arterial stenting. Only experienced interventionalists have been

invited to participate in CREST. In addition, all participating interventionalists will be required to complete training before enrolling patients in the lead-in/credentialing phase of CREST. Once they have completed the training, all investigators must demonstrate that they can perform carotid stenting with an acceptable complication rate prior to enrolling patients in the randomized phase. Transition to the randomized component of the clinical trial will be evaluated on a site-by-site basis by the applicable CREST Committees.

Confidentiality of patient computer data is protected by the use of passwords, data encryption and secure, limited access storage. The SDMC has programs, policies and facilities in use at the present time to ensure the security and confidentiality of the data it manages.

The SDMC and the DSMB play key roles in detecting any hazards the study may pose for its participants. Data are routinely collected and regularly monitored to document morbidity or mortality associated with study-related procedures in each clinic. Timely reports will be made to the DSMB. In addition, the SDMC is responsible for calling the Board's attention to significant interim developments. Results for the different clinics are compared to identify the sources and causes of any remarkable trends from the average performance.

The DSMB is responsible for advising early termination of the trial in the event that unexpectedly large treatment differences provide overwhelming evidence in favor of one intervention before the scheduled end of the trial. It will be the responsibility of the DSMB to review the data and establish limits of safety for the trial, as well as its termination.

12.5 RISKS VERSUS BENEFITS

Carotid revascularization, by means of CEA, prevents stroke and saves lives in some classes of patients. CAS is a relatively new form of carotid revascularization that avoids regional or general anesthesia as well as an incision in the neck. If its effectiveness is comparable to that of CEA, it may be more acceptable to patients and referring physicians. CAS may also be possible in a broader spectrum of patients than CEA.

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APPENDIX A SAMPLE INFORMED CONSENTS

Lead-In Phase

Carotid Revascularization Endarterectomy Stenting Trial (CREST)

1.0 Introduction

You have been invited by your doctor to join in a research study. The study is sponsored by the National Institute of Neurological Disorders and Stroke (NINDS). The study will involve 4300 research participants in the United States and Canada. 1800 participants will be enrolled in this lead-in phase of the study, and 2500 participants will be enrolled in the randomized phase of the study. Healthy brain tissue is dependent upon an adequate blood supply from the carotid arteries (blood vessels in your neck that supply blood to your brain). A narrowing in your carotid arteries, if severe enough, can cause temporary or permanent brain damage (a stroke) by cutting off the blood supply to part of the brain. Your doctor believes that some kind of treatment is necessary to prevent a stroke.

2.0 Purpose

This study will have two phases. **The first phase is called the lead-in phase.**

If you agree to participate as a lead-in patient, you will receive a carotid stent. Carotid stenting is when a metal device called a stent is placed in the narrowed part of your carotid artery to hold it open. As part of the procedure to implant the carotid stent, your physician may choose to use a device called an embolic protection device The embolic protection device is designed to capture material (called embolic material) that could break off from the narrowed area in your carotid artery. Embolic material could block blood flow to the arteries beyond the narrowing and be harmful to the brain.

The lead-in phase of this study is being conducted for a number of reasons. One is to make sure research participant treatment is the same at all research centers and to collect information on the carotid stent procedure and the use of the embolic protection system**.**

The lead-in phase will also allow a review of participating physicians who have been previously trained in use of both devices. The doctor performing your procedure was specifically chosen to participate in this study because he or she has previous experience and is skilled placing stents in the carotid artery. In addition, any doctor chosen to participate in this study has been extensively trained in the use of the stent and the Embolic Protection System. All physicians will be closely monitored during the study.

The carotid stent and embolic protection procedures are under investigation in this study. Although the carotid stent system and embolic protection device are not yet approved for general use by the Food and Drug Administration (FDA), these devices are approved for use in this study.

The second phase of the study will compare results of treating blockages in carotid arteries with either carotid endarterectomy (surgery) or carotid stenting. Carotid endarterectomy is an operation on the carotid artery where the thickened area of the artery is removed through an incision in the neck under general or local anesthesia. During the second phase, neither the research participant nor doctor will know which of

the two therapies will be done, until after the participant has consented to participate in the study and is assigned (similar to flipping a coin) to one of the two treatments.

Most hospitals participating in the study will be enrolling research participants into the lead-in phase before the second phase or general enrollment begins. Information collected during your participation in the study as a "lead-in" research participant may be analyzed separately or together with the information gathered from the non lead-in research participants.

It is important that you read and understand several general principles, which apply to all who take part in this study:

(a) Your participation in the study is entirely voluntary. You should read the information in this consent and ask your doctor, or the study staff who explains it to you, any questions you have before you decide to participate.

(b) Personal benefits to you may or may not result from taking part in the study, but knowledge may be gained from your participation that will benefit others.

(c) You may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled.

(d) You will be told about any new information discovered during the course of this study that may affect your willingness to continue participating in the study.

3.0 Procedures

If you decide to participate in this study your doctor will review the entire procedure with you. A general description of what you will experience is described below.

Before the procedure:

As early as forty-eight hours before the procedure, you will be required to take aspirin and other medication in preparation for your procedure. These medications are intended to prevent your blood from clotting and will be prescribed by your doctor. The day of your procedure, an intravenous line will be started to give you fluids and medicines for sedation and pain prevention.

During the procedure:

Your skin will be numbed (medication like that used by dentists will be injected into your groin) and a catheter (small plastic tube) will be placed in an artery in the groin. Using x-ray visualization (fluoroscopy), the catheter-wire system is advanced to the arteries that supply blood to the brain and contrast material (x-ray dye) is injected to obtain pictures of these arteries (angiogram). Your doctor will use embolic protectionunless he or she believes it may be unsafe because of your anatomy or medical condition. The system will be advanced through the existing catheter, positioned beyond the narrowed section of your carotid artery, and expanded so that it can capture embolic material. The narrowing in your carotid artery may then be dilated (enlarged) with a balloon catheter, if needed. The stent will then be placed in the narrowed area.

The carotid stent is an elastic-like metallic scaffold that has been placed onto a catheter (a small plastic tube) and covered with a retractable sheath (cover), to hold it in place while it is being positioned in the carotid artery. When the stent is positioned across the narrowed carotid artery segment, it is released by pulling back on the sheath and allowed to expand on its own. When released, the stent presses against the artery wall to enlarge the blood vessel at that point of narrowing and may prevent the fatty deposits on the artery wall from breaking off and possibly causing a stroke. The catheter is then removed and another balloon catheter may be used to further expand and enlarge the narrowed portion of the artery. If used, the embolic protection device will then be closed and removed, leaving only the stent in place. Over a period of three to four weeks, the inner lining of the artery will grow over the stent surface and the stent will become a permanent part of your artery.

After the procedure:

You will be required to take medications for a period of four weeks (either clopidogrel 75 mg daily, or ticlopidine 250 mg 1 -2 tablets daily). You will also be required to take aspirin 325 mg 1-2 tablets daily for the first 30 days, and aspirin 325 mg daily thereafter. A lower amount of aspirin may be substituted if you can not tolerate the higher dose of aspirin. For the first four weeks, the combination of two medicines keeps formation of blood clots to a minimum. Thereafter, taking aspirin will be required for at least one year and possibly longer. In addition to these your physician may ask you to take other medications, such as medicine to control blood pressure.

After hospital discharge:

You will need to return to your doctor's office for a follow-up examination at one month and again at 12 months. At the time of this visit, you will be asked about any symptoms you may have experienced. You will have a carotid duplex ultrasound performed immediately after the stent procedure (any time between 1 day to 30 days) and again at the 12-month visit. For this test, a probe is placed against the outside of your neck, over the carotid artery. Sound waves from the probe are bounced off the artery to produce an image of the blood flowing through the artery. If you are taking ticlopidine, you will have blood tests at two weeks and one month. Other tests may be ordered by your physician as a routine part of your care.

4.0 Potential Risks

Procedure Risks:

The risks associated with the stent procedure (which uses the carotid stent system and may include the embolic protection device) include minor stroke (symptoms go away within 30 days), major stroke, death, contrast material (x-ray dye) or drug allergic reaction, kidney failure, bleeding, infection, or blockage to the artery in the leg requiring surgical repair, need for blood transfusion, low blood pressure, and abnormal heart rhythms. Risks that may be associated with the embolic protection device are: thrombosis of the filter, filter entanglement on the stent or other damage to the stent and mechanical failure of the device. On very rare instances, filter entanglement with the stent or failure to recover the filter could result in the filter coming off and remaining

inside the vessel. In such a case, your physician would use additional interventions to remove the filter or stabilize it in the vessel so that it does not obstruct blood flow. This could include surgery of the carotid artery to remove the basket, or placing another stent to compress the filter against the vessel wall, or other maneuvers as determined by your physician.

There may be discomfort or bleeding at the site of insertion of the catheter into the artery. The enlarging of the carotid artery may cause damage to the blood vessels resulting in bleeding or vessel narrowing. Depending on severity and the area of the brain involved, either of these complications could result in worsening neurologic function or death. There is a chance that the stent could be released before it reaches the narrowed vessel segment. Release of the stent before it reaches the narrowed part of the artery rarely produces a bad clinical result. It may be necessary to place another stent in the proper place. The presence of another stent with more stent material may slightly increase the risk of blood clots forming. The stent was designed to expand to fit the size of the artery, however, the rare possibility exists that the stent could migrate (move) following its placement. Depending on the location of the stent is, your doctor may leave the stent where it is, or may perform another procedure to remove or replace it.

The stent is a foreign body. Although metals such as those used to make stents have been implanted for years in human tissues, including blood vessels of the heart, kidneys and legs, there is no long-term information regarding potential side effects of use of such metals in the carotid artery. Some research participants may be allergic to the contrast material (x-ray dye) or other medications used during the procedure. Occasionally contrast material, or drugs may cause damage to other tissues or organs. Such damage could result in minor or serious injury or even death.

Medication Risks:

Aspirin will be used for at least one year after your procedure. Side effects from this medication which may occur include bleeding (which may be minor, major, or life-threatening) or a drop in platelet count (cells that help the blood clot). It may rarely cause a stomach ulcer (bleeding or non-bleeding) or other bleeding problem. If bleeding or a drop in platelet count occurs or it is necessary to perform surgery, it may be necessary to give you blood transfusions or platelet transfusions. Research participants who receive a stent are usually treated with clopidogrel, a mild blood thinner which is similar to aspirin. Clopidogrel may also cause bleeding problems.

It may be necessary for your doctor to prescribe ticlopidine instead of clopidogrel. This medicine can cause bleeding problems. In 1-2% of people, ticlopidine may decrease the number of white blood cells in the body and result in serious infections and, very rarely, death. The white blood cell count will usually return to normal after ticlopidine is stopped. If bleeding or a drop in platelet count occurs or it is necessary to perform surgery, it may be necessary to give you blood transfusions or platelet transfusions.

If your doctor prescribes ticlopidine, a blood sample will be drawn at two and four weeks while you are taking the medicine. You may have discomfort due to taking a blood sample. However, blood samples are necessary to monitor your white blood count.

Other Risks:

Even with a successful stent procedure, there is a chance that the treated area could become narrowed again. This may require additional treatment, such as repeat angioplasty and/or surgery to reduce the chance of stroke that can be caused by the re-narrowing.

This stent procedure may involve additional risks to you, the nature of which are unknown. In addition, this procedure may involve unforeseeable risks to you or your fetus if you are pregnant. Therefore, pregnant women are excluded from this study. Should you become pregnant while taking part in this study, you must immediately notify your doctor.

5.0 Potential Benefits

Research studies such as this are performed to determine the relative risks and benefits of a specific medical treatment and or device. No benefit can be guaranteed by your participation in this study.

6.0 Confidentiality

Your participation in this study will be confidential. When results of a study such as this are reported in medical journals or at meetings, the identification of research participants taking part is withheld. In addition, medical records of all participants are maintained according to current legal requirements. Your records will be made available for review to the Food and Drug Administration (FDA), other applicable government regulatory agencies, the study sponsors (National Institutes of Neurological Disorders and Stroke (NINDS) and the University of Medicine and Dentistry of New Jersey) or their representatives, and the device manufacturer, Abbott Vascular, or its successors or representatives, as required for purposes of this study.

7.0 Permission to Use and Disclose Protected Health Information

What is the purpose of disclosure?

We would like to use your health information for research. This information may include data that identifies you. Please carefully review the information below. If you agree that we can use your personal health information, you must sign and date this form to give them your approval. The federal Health Insurance Portability and Accountability Act (HIPAA) of 1996 requires us to get your approval to use health information about you that we either create or use as part of research. This approval is called an Authorization.

What personal health information do the researchers want to use?

The researchers want to copy and use the portions of your medical record that they will need for their research. If you enter this research study, information that will be used and/or released may include the following: we will use your research record related information from your medical record, results of laboratory tests, case report forms, and both clinical and research observations made while you take part in the research. Clinical information collected will include all information collected during the research as described in this consent form, any medical procedures you undergo, new diagnoses, reported symptoms, changes in body appearance, how well you feel physically and

emotionally and what medications you are prescribed. It also includes reimbursement information such as copies of bills for hospital care, physician services, outpatient services, laboratory tests, diagnostic procedures, home care services and drugs.

Why do the researchers want my personal health information?

We will use your health information to conduct the study, to monitor your health status, to measure the effects of procedures, to determine the research results, and possibly to develop new studies, tests, procedures, and commercial products. Health information is used to report results of research to sponsors and federal regulators. Your personal health information may be seen by auditors to make sure we are following regulations, policies, and study plans. You have the right to look at your study information at the study doctor's office and to ask for corrections of any of your information that is wrong.

We will make every effort to keep information we learn about you private. Sometimes, however, because research involves gathering, recording, and transferring information that needs to be verified, other people besides the researchers at this hospital may need to see the information. These others are listed on this form. Some of these people may share your health information with someone else. If they do, the same laws that the hospital or clinic must obey to protect your health information may not apply to these other people or institutions.

We will share your health information with people at this university clinic or hospital who help with the research. We may share this information with other researchers outside this hospital, or with others who are in charge of the research, who pay for or work with us on the research, or those who make sure that we do this research properly. This authorization form will explain how your personal medical information will be used and shared (disclosed) in this research study.

Who may see your personal health information for this research study:
To meet regulations or for reasons related to this study as noted above, the study team may share a copy of this consent form, your medical records and other records that identify you with the following people:

- The Institutional Review Board – a committee that reviews research studies for the protection of the people who participate in research.
- The United States Food and Drug Administration – the government agency that reviews all research information for approval of new drugs and treatments for the public.
- Department of Health and Human Services—government agency that oversees and funds research involving human beings.
- Office for Human Research Protections (OHRP) (regulatory agency that oversees human subject research)
- Laboratories and other individuals and organizations that look at health information in connection with this study, in agreement with the study's protocol;
- The Sponsors of the study NINDS and the University of Medicine and Dentistry of New Jersey (UMDNJ) and its agents and or contractors including Harvard Clinical

Research Institute, the University of Alabama and Bailer Research to follow how the study is done and to analyze and report the results from the study;

- The device manufacturer, Abbott Vascular or its successors, and their agents and/or contractors to evaluate medical records relating to device problems or unanticipated adverse device events.
- The Principle Investigator, other Investigators, Study Coordinators, and all administrative staff in charge of doing all the work for the study and other research activities;
- Data Safety Monitoring Boards and Clinical Events Committee (a group of people who examine the medical information during the study) and other government agencies or review boards who watch over the safety, success and how the research is done.
- Your personal health information may be seen by auditors from this institution, the sponsor or from government agencies to make sure we are following regulations, policies, and study plans.

You have the right to look at your study information at the study doctor's office and to ask (in writing) for corrections of any of your information that is wrong.

8.0 Alternative Courses of Treatments

Alternative treatments are available. If the narrowing of your carotid artery is associated with symptoms such as weakness or numbness on one side, trouble speaking, walking, or loss of vision, correction of the carotid narrowing can also be performed with an operation on the carotid artery where the thickened area of the artery is removed through an incision in the neck under general or local anesthesia. Even if you do not have such symptoms, the narrowing of your carotid artery could also be treated with an operation on the carotid artery. Another alternative therapy is medical treatment with either anti-platelet or anticoagulant drugs such as aspirin that help to slow down the clotting process and help reduce the risk of stroke. If you do not wish to participate in this study, you may choose to undergo surgical or other medical treatment if appropriate. Your doctor can discuss any alternatives as they apply to your individual situation.

9.0 Policy Regarding Research-Related Injury

In the event of physical or psychological injury resulting from your participation in this study, treatment will be available. There will be no monetary compensation or subsidized medical treatment or compensation either for lost wages provided to you by any person involved in this research project including the study sponsors or device manufacturer or (Name of the institution). ((Name of the institution) will provide the medical and ancillary services ordered by your doctor at the established charges for those services.

10.0 Payments (cost to research participants)

There are no payments to research participants in this study. All medical care costs will be the responsibility of you and your insurance company and will not be assumed by this institution, the NIH, the University of Medicine and Dentistry of New Jersey (UMDNJ)

or Abbott Vascular or its successors. The routine cost for the stent procedure will either be billed to your insurance carrier or your national health service such as Medicare, as applicable.

11.0 Problems or Questions

Your treatment will be supervised by Dr._____CREST Investigator,

at phone number ( ) _____-_____. Any questions or concerns regarding the conduct of this study at this time or in the future should be discussed with him/her. If any problems or questions arise during the course of this study, regarding your rights as a participant in clinical research, or with regard to any research-related injury, you should contact the CREST Primary Investigator, Dr. Robert Hobson, II (Phone) 973-972-7718

You may also contact the Chairman of the Institutional Review Board at:

_____	_____
Name	Institution Name
_____	_____
Address	Telephone Number

Your doctor reserves the right to terminate this study, or your individual participation, at any point if he or she believes that important adverse events might result from its continuation. As stated on the first page of this consent, your participation in this study is voluntary, and you may refuse to participate or withdraw at any time without penalty or loss of benefits. If you choose to withdraw from the study, it is important that you see a doctor for your carotid artery disease and that you continue treatment to prevent a stroke.

11.0 Research Participant's Consent

My signature indicates that I have decided to participate in this study, having read and understood the information provided above. I have received a copy of this informed consent and have been advised to keep it for my later reference and personal records. In particular, I understand that no guarantee or assurance can be made regarding the outcome of my treatment by carotid stenting. Additionally, my signature authorizes release of medical information and records related to this study. A copy of this signed consent form is required to be a permanent part of my medical records throughout my hospitalization at _____ Hospital, and on subsequent charts should I have to be readmitted while in this particular study.

Signature of Participant	Date
Signature of Investigator	Date
Signature of Witness	Date

APPENDIX A SAMPLE INFORMED CONSENTS

Randomized Clinical Trial

Carotid Revascularization Endarterectomy – Stenting Trial (CREST)

1.0 Introduction

You have been invited by your doctor to join in a research study. This study is sponsored by the National Institute of Neurological Disorders and Stroke (NINDS). The study will involve over 4300 research participants in the United States and Canada, 2500 participants will be enrolled in this randomized phase of the study, and 1800 participants will be enrolled in the lead-in phase of the study. Healthy brain tissue is dependent upon an adequate blood supply from the carotid arteries (blood vessels in your neck that supply blood to your brain). A narrowing in your carotid arteries, if severe enough, can cause temporary or permanent brain damage (a stroke) by cutting off the blood supply to a part of the brain. Your doctor believes that some kind of treatment is necessary to prevent a stroke.

2.0 Purpose

Carotid endarterectomy is an operation on the carotid artery where the thickened area of the artery is removed through an incision in the neck and is performed under general or local anesthesia. Carotid stenting is a procedure where a metal device called a stent is placed in the narrowed part of your carotid artery to hold it open and is performed under local anesthesia. As part of the procedure to implant the carotid stent, a device called an embolic protection device may be used. The embolic protection device is designed to capture material (called embolic material) that could break off from the narrowed area. Embolic material could block blood flow to the arteries beyond the narrowing and be harmful to the brain.

The purpose of this study is to compare the results of treating blockages in carotid arteries with either carotid endarterectomy (surgery) OR carotid stenting with or without the use of the embolic protection device. The carotid stent and embolic protection procedures are under investigation in this study. Although the carotid stent system and embolic protection device are not yet approved for general use by the Food and Drug Administration (FDA), these devices are approved for use in this study.

In this study, you have an equal chance of receiving either treatment. Neither you nor your doctor will know which of the two treatments will be done, until after you have consented to participate in the study and you are assigned (similar to flipping a coin) to one of the two treatments.

The doctor performing your procedure was specifically chosen to participate in this study because he or she has previous experience and is skilled at performing the procedure.

It is important that you read and understand several general principles, which apply to all who take part in this study:

(a) Your participation in the study is entirely voluntary. You should read the information in this consent and ask your doctor, or the study staff who explains it to you, any questions you have before you decide to participate.

(b) Personal benefits to you may or may not result from taking part in the study, but knowledge may be gained from your participation that will benefit others.

(c) You may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled.

(d) You will be told about any new information discovered during the course of this study that may affect your willingness to continue participating in the study.

3.0 Study Procedures

Carotid Endarterectomy

Carotid endarterectomy is an operation in which the thickened area (plaque) of the artery is removed through an incision in the neck. Carotid endarterectomy combined with medication is often the standard treatment for select patients with carotid narrowing. This surgery has been shown to reduce the risk of stroke and death, compared to medications alone, in some patients with narrowed carotid arteries. If you are assigned carotid endarterectomy, your doctor will review the entire surgical procedure with you. A general description of what you will experience is described below.

Before the endarterectomy procedure:

Forty-eight hours before the procedure, you will be required to take aspirin in preparation for your procedure. This medication is intended to prevent your blood from clotting and will be prescribed by your doctor. The day of your procedure, an intravenous line will be started to give you fluids and medicines for sedation and pain prevention. Carotid endarterectomy consists of surgical removal of the plaque (artery blockage) and is performed under general anesthesia (while you are asleep) or local anesthesia (medication injected into your neck like that used by dentists). Your doctor and anesthesiologist will decide which form of anesthesia is best for you.

During the endarterectomy:

Your surgeon will make an incision in your neck to expose your carotid artery. The surgeon will then open up the artery and remove the fatty plaque that is attached to the artery wall. The artery and then the incision will be sewn closed.

After endarterectomy:

After your surgical procedure, your doctor will have you take aspirin (325 mg tablet) daily for at least one year. In addition to this, your doctor may ask you to take other medications, such as medicine to control blood pressure.

Carotid Stenting

Carotid stenting consists of placing a metal device called a stent in the narrowed part of the artery to hold it open. If you are assigned to have carotid stenting, your doctor will

review the entire procedure with you. A general description of what you will experience during the stenting procedure is described below.

Before the stent procedure:

As early as forty-eight hours before the procedure, you will be required to take aspirin and other medications in preparation for your procedure. These medications are intended to prevent your blood from clotting and will be prescribed by your doctor. The day of your procedure, an intravenous line will be started to give you fluids and medicines for sedation and pain prevention.

During the stent procedure:

Your skin will be numbed (medication like that dentists use will be injected into your groin) and a catheter (small plastic tube) will be placed in an artery in the groin. Using x-ray visualization (fluoroscopy), the catheter-wire system is advanced to the arteries that supply blood to the brain and contrast material (x-ray dye) is injected to obtain pictures of these arteries (angiogram). Your doctor will use embolic protection unless he or she believes it may be unsafe due to your anatomy or medical condition. The system will be advanced through the existing catheter, positioned beyond the narrowed section of your carotid artery, and expanded so that it can capture embolic material. The narrowing in your carotid artery may then be dilated (enlarged) with a balloon catheter, if needed. The stent will then be placed in the narrowed area.

The carotid stent is an elastic-like metallic scaffold that has been placed onto a catheter (a small plastic tube) and covered with a retractable sheath (cover), to hold it in place while it is being positioned in the carotid artery. When the stent is positioned across the narrowed carotid artery segment, it is released by pulling back on the sheath and is allowed to expand on its own. When released, the stent presses against the artery wall to enlarge the blood vessel at that point of narrowing and may prevent the fatty deposits on the artery wall from breaking off and possibly causing a stroke. The catheter is then removed and another balloon catheter may be used to further expand and enlarge the narrowed portion of the artery. If used, the embolic protection device will then be closed and removed, leaving only the stent in place. Over a period of three to four weeks, the inner lining of the artery will grow over the stent surface and the stent will become a permanent part of your artery.

After the stent procedure:

You will be required to take medications for a period of four weeks (either clopidogrel 75 mg daily, or ticlopidine 250 mg 1 -2 tablets daily). You will also be required to take aspirin 325 mg 1-2 tablets daily for the first 30 days, and aspirin 325 mg daily thereafter. A lower amount of aspirin may be substituted if you can not tolerate the higher dose of aspirin. For the first four weeks, the combination of two medicines keeps formation of blood clots to a minimum. Thereafter, taking aspirin will be required for at least one year and possible longer. In addition to these, your doctor may ask you to take other medications, such as medicine to control blood pressure.

4.0 Follow-up Requirements

After hospital discharge:

Whether you have carotid surgery or carotid stenting, you will need to return to visit your doctor for follow-up examinations at one month, six months, twelve months after your were treated, and every six months thereafter until you are notified by your doctor that the study is completed.

At the time of these visits, you will be asked about any symptoms you may have experienced. If you are taking ticlopidine, you will have blood tests at two weeks and one month. You will have additional blood tests at six months, 12 months and then every year until the study is complete. You will also have a carotid duplex ultrasound performed at some of these visits. For this test, a probe is placed against the outside of your neck, over the carotid artery. Sound waves from the probe are bounced off the artery to produce an image of the blood flowing through the artery.

You will receive phone calls from the study nurse at three months and nine months after you were treated, and every six months thereafter until your doctor notifies you that the study is completed. Additionally, a designated study staff member will contact you by phone at two weeks after your study treatment. During this call you will be asked a set of standard questions regarding your well-being and state of health known as a Quality of Life questionnaire. Other tests may be ordered by your doctor as a routine part of your care.

This study contains a health economics review that will be done to assess for reasonable medical expenses, which occur as a direct result of your participation in this clinical trial. Representatives of the Economic and Quality of Life Assessment Group of the Harvard Clinical Research Institute (HCRI) may obtain copies of the signature page of this informed consent in order to collect hospital bills from the Patient Accounting Department at any hospital to which you are admitted from the time of enrollment in CREST through the study follow-up period.

SUMMARY OF REQUIRED FOLLOW-UP VISITS AND PROCEDURES	
Contact Period	**Required Follow-up**
Two weeks	*Blood tests:* If required by prescribed medications. *Telephone contact:* QOL questionnaire by core lab designee.
One-month	*Doctor's office visit*: Medical history, neurological examination, completion of study questionnaires, carotid duplex ultrasound, ECG and blood tests.
Three months	*Telephone contact:* Medical history and completion of study questionnaire.
Six-months	*Doctor's office visit:* Medical history, neurological examination, completion of study questionnaires, carotid duplex ultrasound and blood tests.
Nine months	*Telephone contact:* Medical history and completion of study questionnaire.
12 months (plus once a year until study exit)	*Doctor's office visit*: Medical history, neurological examination, completion of study questionnaires, carotid duplex ultrasound and blood tests.
15 months (plus every 6 months until study exit)	*Telephone contact:* Medical history and completion of study questionnaire.
18 months (plus once a year until study exit)	*Doctor's office visit*: Medical history, risk factor profile, and completion of study questionnaires.

5.0 Potential Risks

Carotid Endarterectomy

When carotid endarterectomy is performed by a highly experienced surgeon on patients who are at low risk for surgical complications, the risk of minor stroke (symptoms go away in 30 days) or major stroke is less than 5% and chance of death is between 1-2%. There may be discomfort at the site of the surgical incision. Surgery may cause damage to the blood vessels resulting in bleeding or vessel narrowing. Depending on the severity and area of brain involved, either of these complications could result in worsening neurologic function or death.

There may be discomfort at the site of the surgical incision. Wound complications including moderate bleeding and infection may occur in a small number of cases (less than 5%).

Additional risks associated with carotid endarterectomy or anesthesia include, temporary or permanent damage to nerves in your face, lung infection, heart attack, kidney failure, low blood pressure, abnormal heart rhythms, and death.

Medication risks:

Aspirin will be used for at least one year after your procedure. Side effects from this medication which may occur include bleeding (which may be minor, major, or life-threatening) or a drop in platelet count (cells that help the blood clot). It may rarely cause a stomach ulcer (bleeding or non-bleeding) or other bleeding problems. If bleeding or a drop in platelet count occurs or it is necessary to perform surgery, it may be necessary to give you blood transfusions or platelet transfusions.

The treatment (surgery) may involve additional risks to you, the nature of which are unknown. In addition, this procedure may involve unforeseeable risks to you or your fetus if you are pregnant. Therefore, pregnant women are excluded from this study. Should you become pregnant while taking part in this study, you must immediately notify your doctor.

Carotid Stenting

The risks associated with the stent procedure (which uses the carotid stent system and may include the embolic protection device) include minor stroke (symptoms go away within 30 days), major stroke, death, contrast material (x-ray dye) or drug allergic reaction, kidney failure, bleeding, infection, or blockage to the artery in the leg requiring surgical repair, need for blood transfusion, low blood pressure, and abnormal heart rhythms. Risks that may be associated with the embolic protection device are: thrombosis of the filter, filter entanglement on the stent or other damage to the stent and mechanical failure of the device. On very rare instances, filter entanglement with the stent or failure to recover the filter could result in the filter coming off and remaining inside the vessel. In such a case, your physician would use additional interventions to remove the filter or stabilize it in the vessel so that it does not obstruct blood flow. This could include surgery of the carotid artery to remove the basket, or placing another stent to compress the filter against the vessel wall, or other maneuvers as determined by your physician.

There may be discomfort or bleeding at the site of insertion of the catheter into the artery. The enlarging of the carotid artery may cause damage to the blood vessels resulting in bleeding or vessel narrowing. Depending on severity and the area of the brain involved, either of these complications could result in worsening neurologic function or death. There is a chance that the stent could be released before it reaches the narrowed vessel segment. Release of the stent before it reaches the narrowed part of the artery rarely produces a bad clinical result. It may be necessary to place another stent in the proper place. The presence of another stent with more stent material may slightly increase the risk of blood clots forming. The stent was designed to expand to fit the size of the artery and stay in place, however, the rare possibility exists that the stent could migrate (move) following its placement. Depending on the location of the stent, your doctor may leave it where it is, or perform another procedure to remove or replace it.

The stent device is a foreign body. Although metals such as those used to make stents have been implanted for years in human tissues, including blood vessels of the heart, kidneys and legs, there is no long-term information regarding potential side effects of use of such metals in the carotid artery. Some research participants may be allergic to the contrast material (x-ray dye) or other medications used during the procedure. Occasionally contrast material, or drugs may cause damage to other tissues or organs. Such damage could result in minor or serious injury or even death.

Medication Risks:

Aspirin will be used for at least one year after your procedure. Side effects from this medication which may occur include bleeding (which may be minor, major, or life-threatening) or a drop in platelet count (cells that help the blood clot). It may rarely cause a stomach ulcer (bleeding or non-bleeding) or other bleeding problem. If bleeding or a drop in platelet count occurs or it is necessary to perform surgery, it may be necessary to give you blood transfusions or platelet transfusions. Research participants who receive a stent are usually treated with clopidogrel, a mild blood thinner which is similar to aspirin. Clopidogrel may also cause bleeding problems.

It may be necessary for your doctor to prescribe ticlopidine instead of clopidogrel. This medicine can cause bleeding problems. In 1-2% of people, ticlopidine may decrease the number of white blood cells in the body and result in serious infections and, very rarely, death. The white blood cell count will usually return to normal after ticlopidine is stopped. If bleeding or a drop in platelet count occurs or it is necessary to perform surgery, it may be necessary to give you blood transfusions or platelet transfusions.

If your doctor prescribes ticlopidine, a blood sample will be drawn at two and four weeks while you are taking the medicine. You may have discomfort due to taking a blood sample. However, blood samples are necessary to monitor your white blood count.

Other Risks:

Even with a successful procedure, stenting or surgery, there is a chance that the treated area could become narrow again. This may require additional treatment, such as repeat angioplasty and/or surgery to reduce the chance of stroke that can be caused by the re-narrowing.

This treatment may involve additional risks to you, the nature of which are unknown. In addition, this procedure may involve unforeseeable risks to you or your fetus if you are pregnant. Therefore, pregnant women are excluded from this study. Should you become pregnant while taking part in this study, you must immediately notify your doctor.

6.0 Potential Benefits

Research studies such as this are performed to determine the relative risks and benefits of a specific medical treatment and or device. No benefit can be guaranteed by your participation in this study.

7.0 Confidentiality

Your participation in this study will be confidential. When results of a study such as this are reported in medical journals or at meetings, the identification of research participants taking part is withheld. In addition, medical records of all participants are maintained according to current legal requirements.

Your records will be made available for review to the Food and Drug Administration (FDA), other applicable government regulatory agencies, the study sponsors (National Institutes of Neurological Disorders and Stroke (NINDS) and the University of Medicine and Dentistry of New Jersey (UMNDJ)) or their representatives, and the device manufacturer, Abbott Vascular or its successors or representatives, as required for purposes of this study.

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What personal health information do the researchers want to use?

The researchers want to copy and use the portions of your medical record that they will need for their research. If you enter this research study, information that will be used and/or released may include the following: we will use your research record related information from your medical record, results of laboratory tests, case report forms, and both clinical and research observations made while you take part in the research. Clinical information collected will include all information collected during the research as described in this consent form, any medical procedures you undergo, new diagnoses, reported symptoms, changes in body appearance, how well you feel physically and emotionally and what medications you are prescribed. It also includes reimbursement information such as copies of bills for hospital care, physician services, outpatient services, laboratory tests, diagnostic procedures, home care services and drugs.

Why do the researchers want my personal health information?

We will use your health information to conduct the study, to monitor your health status, to measure the effects of procedures, to determine the research results, and possibly to develop new studies, tests, procedures, and commercial products. Health information is used to report results of research to sponsors and federal regulators. Your personal health information may be seen by auditors to make sure we are following regulations, policies, and study plans. You have the right to look at your study information at the study doctor's office and to ask for corrections of any of your information that is wrong.

We will make every effort to keep information we learn about you private. Sometimes, however, because research involves gathering, recording, and transferring information that needs to be verified, other people besides the researchers at this hospital may need to

see the information. These others are listed on this form. Some of these people may share your health information with someone else. If they do, the same laws that the hospital or clinic must obey to protect your health information may not apply to these other people or institutions.

We will share your health information with people at this university clinic or hospital who help with the research. We may share this information with other researchers outside this hospital, or with others who are in charge of the research, who pay for or work with us on the research, or those who make sure that we do this research properly. This authorization form will explain how your personal medical information will be used and shared (disclosed) in this research study.

Who may see your personal health information for this research study:

To meet regulations or for reasons related to this study as noted above, the study team may share a copy of this consent form, your medical records and other records that identify you with the following people:

- The Institutional Review Board – a committee that reviews research studies for the protection of the people who participate in research.
- The United States Food and Drug Administration – the government agency that reviews all research information for approval of new drugs and treatments for the public.
- Department of Health and Human Services—government agency that oversees and funds research involving human beings.
- Office for Human Research Protections (OHRP) (regulatory agency that oversees human subject research)
- Laboratories and other individuals and organizations that look at health information in connection with this study, in agreement with the study's protocol;
- The Sponsors of the study NINDS and the University of Medicine and Dentistry of New Jersey (UMDNJ) and its agents and or contractors including Harvard Clinical Research Institute, University of Alabama and Bailer Research to follow how the study is done and to analyze and report the results from the study;
- The device manufacturer, Abbott Vascular or its successors, and their agents and/or contractors to evaluate medical records relating to device problems or unanticipated adverse device events.
- The Principle Investigator, other Investigators, Study Coordinators, and all administrative staff in charge of doing all the work for the study and other research activities;
- Data Safety Monitoring Boards and Clinical Events Committee (a group of people who examine the medical information during the study) and other government agencies or review boards who watch over the safety, success and how the research is done.
- Your personal health information may be seen by auditors from this institution, the sponsor or from government agencies to make sure we are following regulations, policies, and study plans.

You have the right to look at your study information at the study doctor's office and to ask (in writing) for corrections of any of your information that is wrong.

9.0 Alternative Courses of Treatments

Alternative treatments are available. One alternative is carotid endarterectomy (surgery) as described above. Another alternative is medical treatment with either anti-platelet or anticoagulant drugs such as aspirin that help slow down the clotting process and help reduce the risk of stroke. If you do not wish to participate in this study, you may choose surgery outside of study participation or other medical treatment if appropriate. Your doctor can discuss any alternatives as they apply to your individual situation.

10.0 Policy Regarding Research-Related Injury

In the event of physical or psychological injury resulting from your participation in this study, treatment will be available. There will be no monetary compensation or subsidized medical treatment or compensation either for lost wages provided to you by any person involved in this research project including the study sponsors or device manufacturer or (Name of the institution). (Name of the institution) will provide the medical and ancillary services ordered by your doctor at the established charges for those services.

11.0 Payments (cost to research participants)

There are no payments to research participants in this study. All medical care costs will be the responsibility of you and your insurance company and will not be assumed by this institution, the NIH, the University of Medicine and Dentistry of New Jersey (UMDNJ) or the Abbott Vascular or its successors. The routine cost for this procedure will be billed to your insurance carrier or national health service such as Medicare, as applicable.

11.0 Problems or Questions

Your treatment will be supervised by Dr. _____, CREST Investigator.

at phone number ( ) _____-_____. Any questions or concerns regarding the conduct of this study at this time or in the future should be discussed with him/her. If any problems or questions arise during the course of this study, regarding your rights as a participant in clinical research, or with regard to any research-related injury, you should contact the CREST Primary Investigator, Dr. Robert Hobson (Phone) 973-972-7718

You may also contact the Chairman of the Institutional Review Board at:

_____	_____
Name	Institution Name
_____	_____
Address	Telephone Number

Your doctor reserves the right to terminate this study, or your individual participation, at any point if he or she believes that important adverse events might result from its continuation. As stated on the first page of this consent, your participation in this study is voluntary, and you may refuse to participate or withdraw at any time without penalty or loss of benefits. If you choose to withdraw from the study, it is important that you see a doctor for your carotid artery disease and that you continue treatment to prevent a stroke.

12.0 Research Participant's Consent

My signature indicates that I have decided to participate in this study, having read and understood the information provided above. I have received a copy of this informed consent and have been advised to keep it for my later reference and personal records. In particular, I understand that no guarantee or assurance can be made regarding the outcome of my treatment by carotid stenting. Additionally, my signature authorizes release of medical information and records related to this study. A copy of this signed consent form is required to be a permanent part of my medical records throughout my hospitalization at _____ Hospital. and on subsequent charts should I have to be readmitted while in this particular study.

Signature of Participant	Date
Signature of Investigator	Date
Signature of Witness	Date

APPENDIX B SELECTION OF LEAD-IN PATIENTS AND CLINICAL FOLLOW-UP

Candidates for the lead-in phase of this trial must meet all of the following criteria.

Lesion eligibility is established by angiography using NASCET criteria as delineated in *Appendix F*.

For the use of EPD within CREST, refer to section 3.1.3 and *Appendix C.*

B.1.1 Inclusion Criteria

Clinical Inclusions

1. Patient age ≥18 and ≤ 79 years old.
2. Symptomatic patient, as evidenced by transient ischemic attack (TIA), amaurosis fugax, minor or non-disabling stroke (in the hemisphere supplied by the target vessel) within 180 days of the treatment date, or asymptomatic patients meeting angiographic criteria (≥70%). *(Note: a substantial fraction of patients must be symptomatic).*
3. Patient has no childbearing potential or has a negative pregnancy test within one week prior to the study procedure.
4. Patient, and the patient's physician agree to have the patient return for all required clinical contacts following study enrollment.
5. Patient has been informed of the nature of the study, and has provided written informed consent, approved by the appropriate Institutional Review Board (IRB)/Medical Ethics Committee (MEC) of the respective clinical site. (Sample consent - *Appendix A*).

Anatomic Inclusions

The angiogram will be utilized to establish eligibility.

1. Patient has a discrete lesion located in the internal carotid artery (ICA) (with or without involvement of the contiguous common carotid artery (CCA)).
2. Carotid stenosis ≥50% defined angiography in symptomatic patients (based on NASCET Criteria, reference *F*).
3. Carotid stenosis ≥70% defined angiography in asymptomatic patients (based on NASCET Criteria, reference *F*)
4. Target ICA vessel reference diameter must be measured to be ≥4.0 mm and ≤9.0 mm. Target ICA may be reasonably estimated by angiography of the contralateral artery.
5. Patients with bilateral carotid stenosis are eligible. Management of the non-study stenosis may be done in accordance with local PI recommendation. *(Note: Treatment of the non-study artery must take place at least 30 days prior to the CREST lead-in procedure, or >30 days after the study procedure is completed.)*

6. Expected ability to deliver the stent to the lesion (absence of excessive tortuosity).

B.1.2 Exclusion Criteria

Clinical Exclusions

1. Patient has an evolving stroke.
2. Patient has history of intolerance or allergic reaction to any of the study medications, including aspirin (ASA), ticlopidine and clopidogrel. (Patients must be able to tolerate a combination of ASA and ticlopidine OR ASA and clopidogrel)
3. Patient has active bleeding diathesis or coagulopathy or will refuse blood transfusions.
4. Patient with a history of major ipsilateral stroke likely to confound study endpoints.
5. Patient has severe dementia.
6. Patient has a history of spontaneous intracranial hemorrhage within the past 12 months.
7. Patient has had a recent (<7 days) stroke of sufficient size (on CT or MRI) to place him or her at risk of hemorrhagic conversion during the procedure.
8. Patient had hemorrhagic transformation of an ischemic stroke within the past 60 days.
9. Patient has Hgb <10 g/dl, platelet count <125,000/μl, uncorrected INR >1.5, bleeding time >1 minute beyond upper limit normal, or heparin-associated thrombocytopenia.
10. Patient has any condition that precludes proper angiographic assessment or makes percutaneous arterial access unsafe. (e.g., morbid obesity, sustained SBP >180 mm Hg.)
11. Patient has had neurologic illnesses within the past two years characterized by fleeting or fixed neurologic deficit which cannot be distinguished from TIA or stroke (e.g. partial or secondarily generalized seizures; complicated or classic migraine; tumor or other space-occupying brain lesions; subdural hematoma, cerebral contusion or other post-traumatic lesions; intracranial infection; demyelinating disease; moderate to severe dementia; or intracranial hemorrhage).
12. Patient is actively participating in another drug or device trial (IND or IDE) that has not completed the required protocol follow-up period. Patients may be enrolled only once in CREST, and may not participate in any other clinical trial during the CREST follow-up period.
13. Patient has inability to understand and cooperate with study procedures or provide informed consent.

14. If a patient has vertebrobasilar insufficiency symptoms only, without clearly identifiable symptoms referable to the study carotid artery, he/she will be considered an asymptomatic patient for the lead-in phase of the study.
15. Knowledge of cardiac sources of emboli (e.g. left ventricular aneurysm, intracardiac filling defect, cardiomyopathy, aortic or mitral prosthetic heart valve, calcific aortic stenosis, endocarditis, mitral stenosis, atrial septal defect, atrial septal aneurysm, or left atrial myxoma).
16. Chronic atrial fibrillation, known by history or present on entry examination.
17. Any episode of paroxysmal atrial fibrillation within the past 6 months, or history of paroxysmal atrial fibrillation requiring chronic anticoagulation.
18. Patient has had a MI within previous 30 days.
19. Patient has had a recent GI bleed that would interfere with antiplatelet therapy.

Anatomic Exclusions

Specific angiographic criteria are for all lead-in patients.

1. Severe vascular tortuosity or anatomy that would preclude the safe introduction of a guiding catheter, guiding sheath, or stent placement.
2. Presence of a previously placed intravascular stent or graft in the ipsilateral distribution.
3. Presence of extensive or diffuse atherosclerotic disease involving the aortic arch and proximal common carotid artery that would preclude the safe introduction of a guiding catheter or guiding sheath.
4. An intraluminal filling defect (defined as an endoluminal lucency surrounded by contrast, seen in multiple angiographic projections, in the absence of angiographic evidence of calcification) that is not associated with an ulcerated target lesion.
5. Ipsilateral intracranial or extracranial arterial stenosis greater in severity than the lesion to be treated, cerebral aneurysm ≥5 mm, AVM (arteriovenous malformation) of the cerebral vasculature, or other abnormal angiographic findings that constitute contraindication to CAS.
6. Bilateral carotid stenosis if intervention is planned within the 30-day periprocedure period.
7. Occlusion [Thrombolysis In Myocardial Infarction Trial (TIMI 0)] “string sign” >1 cm of the ipsilateral common or internal carotid artery.
8. Well-delineated carotid artery dissection below the carotid siphon.
9. Ostial lesion of LCCA/RCCA.

B.2 CLINICAL AND LABORATORY TESTS

Summary of Required Testing – Lead-In Patients				
Test	**Pre-Procedure**	**Post-Procedure 6-54 hours**	**Post-Discharge 1 Month**	**Post-Discharge 12 Months**
Carotid duplex ultrasound		√[1]	√[1]	√
CT scan/MRI	√[2]		PRN[2]	PRN[2]
TIA/Stroke Questionnaire	√		√	
Neurological exam	√[3]	√[3, 8]	√[3]	√[3]
NIH Stroke Scale (NIHSS)	√[3]	√[3, 8]	√[7]	√[7]
Modified Rankin Scale	√[3]			
Barthel Index	√[3]			
Medical Hx, Risk Factor Profile	√			√
ECG	√	√[4]		
Cardiac Enzymes (CPK, CK-MB or troponin)	√	√[5]		
Lipid Profile	√			
SMAC-7	√			
Fasting Blood Sugar	√			
Cerebral Angiogram	√[6]		PRN	PRN

[1]May be performed between 1 and 30 days post-procedure, exams are to be forwarded to the Core Lab regardless of whether performed by a CREST credentialed laboratory or not.

[2]Most recent pre-procedural neurological image will be used for baseline (if available), and additional CT scans should be performed as needed to evaluate subsequent cerebrovascular events.

[3]Neurological examinations will be performed by the study neurologist or independent neuroscientist/ physician certified in the use of NIHSS. This physician cannot be the one that performed the study procedure on the patient. [4]In addition to ECG 6-48 hours post procedure, an ECG should be obtained for chest pain lasting >15 minutes or for symptoms indicating myocardial ischemia.

[5]In addition to cardiac enzymes (CPK and CK-MB or troponin) 6-8 hours post-procedure, cardiac enzymes q 8 hr x 3 with pathological elevation of post-procedural enzymes, for ECG changes, or chest pain lasting >15 minutes.

[6]May have been performed prior to enrollment to qualify % stenosis and again as part of the procedure.

[7]NIHSS must be performed 3 months after the occurrence of a potential stroke endpoint.

[8]Performed between 18-54 hours post procedure by the study neurologist or independent neuroscientist/ physician.

Pre/Intra Procedure Testing

Lead-in Participants

The following should be performed within **one year** prior to enrollment in the lead-in phase:

- Cerebral angiogram. The angiogram can be performed on the day of procedure. If the angiogram performed on the day of procedure indicates the patient is not eligible, the patient is not enrolled; however, if an adverse event occurs during the angiogram, the patient is enrolled.

The following should be completed **within 180 days** prior to enrollment in the lead-in phase:

- Chemistry profile comprised of a lipid profile (HDL, triglycerides, and total cholesterol estimated LDL) and SMAC-7

The following should be completed **within two weeks** prior to enrollment in the lead-in phase:

- General history, risk factor profile and physical examination (H&P) prior to entering the study.
- Neurological examinations, NIH Stroke Scale, Modified Rankin Scale and Barthel Index performed by study neurologist or independent neuroscientist-physician.
- TIA/Stroke Questionnaire.
- ECG

The following should be completed **within 48 hours** prior to enrollment in the lead-in phase:

- Fasting blood sugar
- Cardiac enzymes: troponin, or CPK including CK-MB fractionation.

If available, the most recent pre-procedural neurological image must be documented in the case report form, and a copy of the image kept on file.

B.3 SUMMARY OF FOLLOW-UP PROCEDURES

Summary of Follow-up Procedures – Lead-In Patients	
Contact Period	**Follow-up**
Post-Discharge (1 day to 30 days)	***Carotid Duplex Examination***
One-month ± one week	***Physician office visit***: Medical history, risk factor profile, neurological examination, NIHSS, TIA/Stroke Questionnaire,
12 months ± two weeks	***Physician office visit***: Medical history, risk factor profile, neurological examination, NIHSS, carotid duplex ultrasound,

APPENDIX C USE OF THE EMBOLIC PROTECTION SYSTEMS WITHIN CREST

Information previously contained within this Appendix is superseded by the Embolic Protection Device manufacturer's product instructions.

Refer to Warnings, Precautions and detailed instructions provided in the manufacturer's Instructions for Use provided with the embolic protection device.

APPENDIX E STATISTICAL ANALYSIS AND POWER CALCULATIONS

A. Analyses for NIH:

1.0 Introduction

The primary goal of CREST is to assess if the efficacy of Carotid Artery Stenting(CAS) differs from that of Carotid Endarterectomy (CEA) over a multi-year time horizon. Endpoints for the study are any stroke, myocardial infarction and death during the 30-day perioperative period, and stroke ipsilateral to the procedure afterward. An intention-to-treat survival analyses will be used to assess this difference.

Secondary outcomes include the evaluation of gender differences in the relative efficacy of CEA versus CAS, the estimation of restenosis rates during the follow-up period, differences in other events or complications between treatments, and assessment of specific events that comprise the composite primary outcome.

The "NIH" goal for CREST is to assess if there is evidence of a difference in event rates between CEA and CAS over a multi-year horizon. In addition to this goal, a separate analysis will be conducted for the regulatory agencies (FDA, etc) that will employ an equivalency analysis approach to assess if there is evidence that CAS is "as good or better" than the standard treatment of CEA at one year.

The statistical approach and power considerations for the clinical trial are also discussed in this appendix.

2.0 Clinical Trial Statistics and Power Considerations

2.1 Primary Endpoint for NIH Analysis

2.1.1 Analysis Approach

The primary goal of CREST is to identify differences between CAS and CEA in preventing endpoint events over a multi-year follow-up. The main comparisons of the groups with respect to the distribution of time until the composite endpoint (as defined above) will be based on survival analyses. These techniques are useful in that they allow for varying lengths of follow-up among study participants and for comparisons to be made over the entire course of the follow-up period. Kaplan-Meier estimates[1] will be made of the survival of both the CAS and CEA groups. Estimates of the proportion of patients who remain free of the composite endpoint at pre-specified (30 days, six months, one year and annually thereafter) time-points, and the associated confidence intervals will be constructed.[2] To compare study groups, anticipate the use of a proportional hazard model[3] if the underlying assumptions appear warranted. The hazard ratio between the groups will be estimated after adjustment for important covariates including age, gender, and an index of stroke severity. We note that these covariates are likely to be distributed equally between the treatments, but covariate adjustment for important covariates remains an important issue to remove bias.[4] Each treatment group is likely to have a high initial hazard (associated with the procedures) followed by lower hazard over the follow-up period; hence, the proportional hazards assumption is likely to be met. Log/log plots of survival will be used to examine the assumption of proportional hazards.[5] Should there be clear evidence that the proportional hazard assumption is not met, alternative

statistical techniques that do not require the assumption will be employed. In the unlikely case of clearly non-proportional hazards, a comparison will be made of the proportion event free at an arbitrary point (i.e., 4 years) following randomization.[6] There is only a marginal loss in power associated with this approach, but it does have the shortcomings of: (1) requiring the selection of the arbitrary point for comparison, and (2) not easily allowing adjustment for covariates. We considered these shortcomings sufficient to suggest that proportional hazards analysis be the primary analysis approach; however, should the proportional hazards assumption be violated, we will adopt this alternate approach.

In order to appropriately assess the peri-operative events, failure time will be measured from the day of the procedure, rather than measuring from the day of randomization. Those participants randomized but not receiving treatment (death or event prior to the procedure, study drop-out prior to procedure, etc.) will be included in the primary analysis according to the intention-to-treat principal, and time to failure will be measured from randomization. This approach potentially introduces minor biases in the unlikely event of an imbalance in the proportion of randomized, but untreated patients between the study arms. This bias will be addressed by minimizing the time between randomization and treatment, and by the institution of a thorough screening and informed consent procedure.

Standard survival methods depend on "non-informative" censoring; i.e. that the subject's time until failure is independent of the censoring mechanism. This assumption may be unwarranted in some situations. Differences in censored versus uncensored subjects will be monitored, and apply techniques as described by Link[7] or Wu and Baily where appropriate.[8]

For purposes of these analyses the symptomatic and asymptomatic patients will be pooled. Although a consistent treatment effect is anticipated by symptomatic status strata, the potential for a differential treatment efficacy between symptomatic and asymptomatic patients will be assessed by the inclusion of interaction terms in the proportional hazards models. The pooling of these populations will result in marginally different event rates than that estimated in previous versions of the protocol, and the event rate will be affected by the proportion of symptomatic/asymptomatic patients.

2.1.2 Sample Size/Power Considerations for the Primary Hypothesis

All hypothesis tests performed during the analysis of the primary and secondary endpoints will be two-sided. This approach has been recommended as being appropriately conservative and sensitive to the possibility that interventions may have unexpected deleterious effects.[9] The alpha level associated with the primary comparison will be 0.05.

CEA event rate. Assumptions for event rates in the symptomatic series were based on the NASCET[10] study and are generally supported by data available from the CREST lead-in series. Specifically we are assuming the peri-procedural event rate of 5.80% observed in NASCET. Only ipsilateral strokes were counted as events after the first 30 days postoperatively. Excluding the peri-operative period, 3.2% of patients had an ipsilateral

stroke over a 23 month period corresponding to an annual stroke rate of approximately 1.68%. Because NASCET and other studies did not systematically collect data on MI events, there was little information on the anticipated MI event rate. As such, previous versions of the protocol conservatively did not include events arising from this source. With data collection from the CREST lead-in series, it is apparent that an event rate of approximately 1% appears reasonable.

A peri-operative event rate of 3.35% is estimated in the asymptomatic population in the CEA arm based on the paper by Rothwell.[21] We have assumed the same ratio of post-operative events to pre-operative events for the asymptomatic patients as seen in NASCET for symptomatic patients – implying a one-year post-procedure event rate of 1.07%, and a one year event rate of 4.42%. There is little evidence of a differential MI event rate from the CREST lead-in series. We have assumed the same proportional treatment difference for asymptomatic patients as observed for symptomatic patients.

Targeted intervention effects. The five-year event rates in ACAS were 5.1% and 11.0%. This difference has been greeted by a spirited discussion of the clinical significance of a difference of this magnitude both at meetings and in the literature.[11] We consider this debate clear empirical evidence that differences of 1.2% per year (or 5.9% over a five-year horizon) are of marginal clinical importance in this arena of patient management. We propose that differences within 5.9% over a five-year period be considered as clinically insignificant. Because the primary analysis tool for the CREST study is proportional hazards analysis (Cox regression), this difference of 1.2% per year must be translated to a corresponding hazard ratio. The original CREST protocol included only symptomatic patients, who have a higher event rate than the asymptomatic patients now permitted for inclusion. The anticipated event rate for CREST with the inclusion of asymptomatic patients is a function of the relative mix of symptomatic and asymptomatic patients. However, the relative effect associated with a 5.9% absolute treatment effect is larger for lower event rates. As such, we can conservatively calculate the relative effect (hazard ratio) associated with a 5.9% absolute treatment effect in the symptomatic patients and be assured that the resulting relative effect is smaller than would result from the inclusion of the asymptomatic patients. That is, the resulting relative effect calculated for symptomatic patients alone is conservative for the purposes of power calculations.

The anticipated 4-year event rate for the CAS arm of CREST is 13.35% $((0.058+0.01)+(1-(1-0.0168)^4) = 0.1335)$. Were only symptomatic patients included, CREST should be powered to detect differences if the CAS event rate is greater than 19.25% (13.35% + 5.9%) or less than 7.45% (13.35% - 5.9%). The conversion of these absolute differences to a relative effect (hazard ratio) can be done under the assumption of exponential survival, where the difference between event rates of 19.25% and 13.35% corresponds to a hazard ratio of $1.49 = (\ln(S_1)/\ln(S_2) = \ln(1-0.1925) / \ln(1-0.1335)=1.49$, and the difference between event rates of 7.45% and 13.35% corresponds to a hazard ratio of 0.54 $(\ln(S_1)/\ln(S_2) = \ln(1 – 0.0608)/\ln(1 – 0.1335) = 0.54)$.

Attrition rates. A 2% annual lost-to-follow-up rate over 4 years would result in a conservative estimate of 7.7% of the total sample size.

Power Formula. Schoenfeld[14] presents a power formula that yields the desired power to test the equality of two survival distributions when the proportional hazards model holds.

Parameters and Assumptions Used in Sample Size Projections

Power to detect hazard ratio of 1.49

For the calculation of the power to detect the hazard ratio of 1.49, assumptions on event rates are shown in Table 1. Included in this table is a brief description of the source of the data or the approach for the calculation of the event rate.

Table 1: Assumed event rates for calculation of HR = 1.49	Symptomatic		Asymptomatic	
	Peri-operative	Post-Operative	Peri-operative	Post-Operative
CEA	6.80% (stroke+death from NASCET + 1% for MI)	1.68% (stroke+death from NASCET)	4.35% (stroke+death from Rothwell + 1% for MI)	1.07% (calculated as the same proportionate increase between peri-operative and post-operative as for symptomatic patients
CAS	9.96% (calculated as an increase associated with a hazard ratio of 1.49: $e^{1.49*\ln(1-0.0680)}$	2.46% (calculated as the same proportionate increase between peri-operative and post-operative as for CEA symptomatic patients	6.41% (calculated as an increase associated with a hazard ratio of 1.49: $e^{1.49*\ln(1-0.0435)}$	1.58% (calculated as the same proportionate increase between peri-operative and post-operative as for symptomatic patients

The event rates provided in Table 1 can be used to calculate the anticipated number of events as shown in Table 2. Here, it is assumed that the event rates in Table 1 apply to the 12 patients recruited during 2002, and the 50 patients recruited during 2003. It has been assumed that the remaining patients will be recruited at a uniform rate over the period from January 2004 through June 2007, and that all patients will be followed until June 2008. Under these assumptions, the number of events and the power to detect the hazard ratio of 1.49 are provided in Table 2. As can be seen, even without the recruitment of asymptomatic patients, if 1,400 symptomatic patients are recruited there will be 180 events and approximately 80% power (76%). However, if 1,100 asymptomatic patients are also recruited, then there will be over 80% power with only 1,000 symptomatic patients, and 90% with 1,400 symptomatic patients.

Table 2: Number of events and power to detect a hazard ratio of 1.49		Number of Asymptomatic Patients			
		0		1100	
		# Events	Power	# Events	Power
# of Symptomatic Patients	1000	130	62%	218	83%
	1200	155	70%	243	87%
	1400	180	76%	267	90%

Power to detect hazard ratio of 0.54

For the calculation of the power to detect the hazard ratio of 0.54, assumptions on event rates are shown in Table 3. Included in this table is a brief description of the source of the data or the approach for the calculation of the event rate.

Table 3: Assumed event rates for calculation of HR = 0.54	Symptomatic		Asymptomatic	
	Peri-operative	Post-Operative	Peri-operative	Post-Operative
CEA	6.80% (stroke+death from NASCET + 1% for MI)	1.68% (stroke+death from NASCET)	4.35% (stroke+death from Rothwell + 1% for MI)	1.07% (calculated as the same proportionate increase between peri-operative and post-operative as for symptomatic patients
CAS	3.73% (calculated as an decrease associated with a hazard ratio of 0.54: $e^{0.54*\ln(1-0.0680)}$	0.92% (calculated as the same proportionate increase between peri-operative and post-operative as for CEA symptomatic patients	2.37% (calculated as an decrease associated with a hazard ratio of 0.54: $e^{0.54*\ln(1-0.0435)}$	0.59% (calculated as the same proportionate increase between peri-operative and post-operative as for symptomatic patients

The event rates provided in Table 3 can be used to calculate the anticipated number of events as shown in Table 4. Here, it is assumed that the event rates in Table 4 apply to the 12 patients recruited during 2002, and the 50 patients recruited during 2003. It has been assumed that the remaining patients will be recruited at a uniform rate over the period from January 2004 through June 2007, and that all patients will be followed until June 2008. Under these assumptions, the number of events and the power to detect the hazard ratio of 0.54 are provided in Table 4. As can be seen, even without the recruitment of asymptomatic patients, even without the recruitment of asymptomatic patients there is 80% power with 1,000 symptomatic patients and 90% power with 1,400 symptomatic patients.

Table 4: Number of events and power to detect a hazard ratio of 0.54		Number of Asymptomatic Patients			
		0		1100	
		# Events	Power	# Events	Power
# of Symptomatic Patients	1000	82	80%	137	95%
	1200	98	86%	152	97%
	1400	114	90%	168	98%

The power to detect differences will also be marginally affected by the "alpha spending" associated with two early interim analyses, performed by the O'Brien-Flemming boundaries; however, the impact of these tests will be marginal.

2.2 Secondary Endpoints

2.2.1 Treatment/Gender Interaction

As noted in the proposal, there appear to be substantial gender differences in the efficacy of endarterectomy. Because this differential efficacy was not anticipated by either the ACAS or NASCET Investigators, these studies have not been designed to appropriately assess the differential effects. However, that this effect has been observed in both ACAS

and NASCET implies that it is imperative to properly assess this effect. This section offers the analysis approach and power to assess this treatment.

The hazard model formula is $h(t) = h_0(t) \exp\{\beta_1 * T + \beta_2 * G + \beta_3 * TG,\}$ where T = Treatment, G = Gender and TG = Treatment*Gender. Let G = - ½ if male and ½ if female. Let T = - ½ if CEA and ½ if CAS. Then the exponent part of the equation takes the following values:

Male, CEA:- ½ β_1 - ½ β_2 + 1/4 β_3 Male, CAS: - ½ β_1 + ½ β_2 - 1/4 β_3

Female, CEA: ½ β_1 - ½ β_2 - 1/4 β_3 Female, CAS ½ β_1 + ½ β_2 + 1/4 β_3

The hazard ratio for the interaction can then be written:

$HR_{TG} = (h(t)_{Male, CEA} / h(t)_{Male, CAS}) / (h(t)_{Female, CEA} / h(t)_{Female, CAS})$

$= \{(h_0(t) \exp\{-1/2*\beta_1 - 1/2*\beta_2 + 1/4*\beta_3) / ((h_0(t) \exp\{-1/2*\beta_1 + 1/2*\beta_2 - 1/4*\beta_3)\}/$

$\{(h_0(t) \exp\{ 1/2*\beta_1 - 1/2*\beta_2 - 1/4*\beta_3) / ((h_0(t) \exp\{ 1/2*\beta_1 + 1/2*\beta_2 + 1/4*\beta_3)\}$

$= \exp\{- \beta_2 + 1/2*\beta_3\} / \exp\{- \beta_2 - 1/2*\beta_3\}$

$= \exp\{\beta_{3\}}$ So, $\beta_3 = \ln (HR_{TG})$

With equal sample size in each group, the general form of the formula for the number of events required to detect a hazard ratio for treatment*gender (HR_{TG}) is: $E_{TG} = (Z_\beta + Z_{1-\alpha/2})^2 / \text{Var(TG)}\ \beta_3^2$. (14, 15) The coding also ensures that the correlation between T and TG and G and TG is zero so that the formula for the number of events is valid. Furthermore, $\text{Var(TG)} = (1/4^2 + 1/4^2 + 1/4^2 + 1/4^2) /4 = 1/16$. so,

$$E_{TG} = (Z_\beta + Z_{1-\alpha/2})^2 / \text{Var(TG)}\ \beta_3^2.$$

$$= 16\ (Z_\beta + Z_{1-\alpha/2})^2 / \ln^2(HR_{TG})$$

where E_{TG} is the number of events and Z_α is from the standard normal distribution.

We have shown in Section 2.1 that the number of events required to detect a hazard ratio for treatment (HR_T) is

$$E_T = 4\ (Z_\beta + Z_{1-\alpha/2})^2 / \ln^2(HR_T)$$

$$= 16\ (Z_\beta + Z_{1-\alpha/2})^2 / 4 \ln^2(HR_T)$$

$$= 16\ (Z_\beta + Z_{1-\alpha/2})^2 / (2 \ln(HR_T))^2$$

$$= 16\ (Z_\beta + Z_{1-\alpha/2})^2 / \ln(HR_T^2)^2$$

Comparing the formula for E_{TG} with the formula for E_T, it can be seen that for a fixed number of events *i.e.* $E_{TG} = E_T$, $HR_{TG} = HR_T^2$. For $HR_T = 1.49$, a HR_{TG} greater than 2.22 (*i.e.* 1.49^2) or smaller than .45 can be detected with 90% power.

2.2.2 Restenosis Rates

One of the important secondary aims of CREST is to estimate the restenosis rates in both the endarterectomy and stenting groups, and to estimate if the restenosis rates are similar between the two treatments. Assessments of differences in the degree of stenosis at the lesion site between two treatment groups will be assessed at 6 and 12 months post-procedure. Differences between the groups will be assessed using ultrasound criteria that will be refined by describing the relationship between angiography and ultrasound in this population. However, the spirit of the assessment of differences between groups will be to assess differences in average percent stenosis between the two groups at follow-up points including six months and one year after statistical adjustment (by analysis of covariance) for observed differences in ultrasound characteristics at one month. Adjustment for the one-month ultrasound is suggested because increased flow at this time point are likely to be associated with hemodynamic disturbances associated with the stent rather than true atherosclerosis.

Restenosis Rate in the CEA Arm	CAS Restenosis Rate detectable with 90% power	
	Lower Rate	Higher Rate
10%	6.4%	14.2%
20%	15.1%	25.4%
30%	24.2%	36.1%

Considering restenosis as a dichotomous (yes/no) outcome, the power to detect differences between treatment groups is a function of the overall restenosis rate, seen in the background section of this protocol to be at approximately 10% to 30%. If the rate in the CEA arm is 10%, a restenosis rate in the CAS arm below 6.4% or above 14.2% can be detected with 90% power (see table). Likewise, if the restenosis rate in the CEA arm is 20%, a CAS rate below 15.1% or above 25.4% can be detected with 90% power. If the rate in the CEA arm is 30%, a rate in the CAS arm below 24.2% or above 36.1% can be detected with 90%. As such, if the rate in CEA arm is 10%, 20% or 30%, a difference of approximately $\pm$ 4%, $\pm$ 5%, and $\pm$ 6% can be detected with 90% power.

2.2.3 Perioperative Event Rates

As a secondary outcome, the proportion of perioperative events (strokes, myocardial infarctions and deaths within 30 days) will be contrasted between the two procedures. Again, the approach is to establish that CAS has event rates that differ substantially from those in the CEA group. Since the perioperative period is short, little censoring is anticipated and categorical methods can be used. Logistic regression techniques will be employed to examine differences between the groups after control for major covariates (as in the primary analysis - age, gender, and stroke severity). As discussed in Section .2.1, we anticipate the perioperative event rate for the endarterectomy arm to be

approximately 6.8% in symptomatic patients (5.8% stroke and death + 1.0% MI) and 4.35% in asymptomatic patients (3.35% stroke and death + 1.0% MI). The overall event rate will be a weighted average of these two, proportionate to the representation of the symptomatic and asymptomatic patients. With the anticipate 1400 symptomatic patients and 1100 asymptomatic patients, the average event rate will be 5.7%.With 1,250 subjects in each group there is 90% power to detect differences between groups if the event rate in the CAS arm is less than 3.2% or greater than 9.3%.

2.2.4 Postoperative Event Rates

Differences in the post-procedural event rates (ipsilateral stroke) between the two study groups will be assessed using proportional hazards models. This analysis will be performed only among those participants surviving the 30-day perioperative period. Similar covariates and analysis will be performed as used for the primary analysis.

The power to detect differences between the two treatments can also be calculated in an approach similar to that for the primary hypothesis. The statistical power is reduced, however, because the perioperative events observed in the study will not be incorporated in this analysis. Using the assumptions and formula from Section 2.1, the annual post-procedural event rate for symptomatic patients is assumed to be 1.68, while the post-procedural event rate for the asymptomatic patients is 1.07. Again, the observed event rate will be a weighted average of these rates, and with 1400 symptomatic and 11000 asymptomatic patients the annual event rate should be approximately 1.41. Applying this event rate to the approximately 2,358 patients who will not have a peri-procedural event ((1.000 – 0.057)*2500), and assuming an average 2-year follow-up for patients, there will be approximately 67 events during follow-up. Using the approach of Schoenfeld, this will provide approximately 80% power to detect a difference between groups if the hazard ratio of CAS-to-CEA is less than 0.50 or greater than 2.00. The corresponding detectable hazards ratios with 90% power are 0.45 and 2.20, respectively.

3.0 Regulatory Agencies

3.0.1. Introduction

The proposed regulatory analysis for CREST is an equivalency formulation for a difference between CEA and CAS treatment event rates. The primary hypothesis will focus on the overall difference in proportions for one-year event rates between CEA and CAS patients. All surviving patients who have not been lost to follow up will be followed a minimum of one year.

The formulation of the hypothesis is like that proposed in the original Blackwelder article [Controlled Clinical Trials 1982;3:345-353], specifically:

$H_O: \pi_{CAS} > \pi_{CEA} + \delta$

$H_A: \pi_{CAS} \leq \pi_{CEA} + \delta$

Where π_{CAS} is the true event rate at one-year for the CAS group, π_{CEA} is the true event rate at one year for the CEA group, and δ is a constant to define a window of equivalency, which has been established to be 2.6% (by binding agreement). Alpha is set at 0.05, Beta is 0.20, and the test assumes a one-sided interval. The event rate is the primary endpoint for the regulatory analysis of periprocedural death, stroke or MI, plus ipsilateral stroke to one year.

The statistical test to address the hypothesis will be implemented by estimating these proportions using Kaplan-Meier estimation with the Greenwood estimate of the standard error, and differences will be tested under the assumption of asymptotic normality via a linear contrast. Appropriate methods will be used to ensure that the assumption of normality is reasonable.

3.0.2. Secondary Endpoint Analyses

In addition to the primary endpoint analysis, several secondary endpoint analyses will be performed as follows:

1. As a secondary hypothesis an equivalency analysis (similar to the primary aim) will be conducted with the strata defined by symptomatic status (i.e., for asymptomatic patients alone, and for symptomatic patients alone).

   The distribution of the proportion of symptomatic and asymptomatic patients recruited to CREST will be determined as a product of the conduct of the study. However, it is anticipated that there will be 1400 symptomatic patients and 1100 asymptomatic patients at the end of the study (the exact distribution will not be known until that time). We are confident that at least 800 patients will be recruited to each strata defined by symptomatic status. The ratio of symptomatic to asymptomatic patients recruited within the study will be monitored by the Statistical Analysis Center to assure a relatively proportionate distribution between each strata in the final study population. The δ supported within the symptomatic and asymptomatic strata is then a function of the achieved sample size for the strata and the δ used in the final analysis will be computed at the conclusion of the study and will be solely a function of the achieved sample size. Again, we anticipate that 1100 asymptomatic and 1400 symptomatic patients will be recruited. However, because of the uncertainty in recruitment the δ will be calculated for symptomatic and asymptomatic strata for a range of sample sizes beginning at 800 and extending to 1700 (the number in the "other" strata if the imbalance is as great as one strata recruiting only 800 patients). For these calculations, alpha = 0.05, beta < 0.20, and one-sided tests are assumed.

2. In addition to the primary analysis focusing on 1-year efficacy, early differences in peri-procedural events will be assessed by focusing on 30-day event rates (e.g., 30 day stroke, myocardial infarction, and death; stroke and death; major stroke and death) using an approach identical to the primary hypothesis.

Additional secondary endpoints that will be addressed as part of the regulatory analysis include specifically:

3. Acute success as defined in Section 4.3.4 of the protocol
4. Target lesion revascularization at 12 months
5. Access site complication requiring treatment
6. Cranial nerve injury unresolved at 1 and 6 months

3.0.3 Other Regulatory Analyses

Supplementary components to the regulatory analysis include the following:

1. In order to assess whether the efficacy is the same for asymptomatic and symptomatic patients, that is it reasonable to "pool" the two populations to produce an overall estimate, a "poolability" analysis will first be performed. In order to estimate this, four Kaplan-Meier estimates will be produced: $CEA_{Asymptomatic}$, $CEA_{Symptomatic}$, $CAS_{Asymptomatic}$, and $CAS_{Symptomatic}$. The similarity of the efficacy can then be tested using a standard test for interaction, specifically:

   $$CEA_{Asymptomatic} - CEA_{Symptomatic} - CAS_{Asymptomatic} + CAS_{Symptomatic} = 0$$

   This interaction test will be implemented under the assumption of asymptotic normality via a linear contrast. Appropriate methods will be used to ensure that the assumption of normality is reasonable. If normality is not substantiated, transformations of the data or non-parametric analyses will be considered. In order to provide a liberal criteria regarding "concern" for interactions, strata-specific analysis will be considered should the interaction test be significant at the 0.1 level

2. Long-term outcomes will be evaluated using a composite measure of all stroke, death, and MI within 30 days, plus ipsilateral strokes beyond 30 days. In order to assess the differences in the durability the differences in the long-term outcome of the CAS versus the CEA patients will be assessed using proportional hazards analysis with differences between groups assessed by an equivalency hypothesis. The hazard ratio will be formulated (without loss of generality) as the h_{CAS} / h_{CEA} (i.e., hazard of stenting relative to endarterectomy).

   Under the equivalency formulation, the null hypothesis is that the "standard" treatment (CEA) is superior to the "new" treatment (CAS) by some constant δ. The alternative hypothesis is the new treatment is "as good or better" than the alternative hypothesis, where "as good" is defined as being within the constant δ.

   With the hazard formulated as stenting relative to surgery, this implies that δ is some number above 1.0, and the hypotheses are:

   $$H_O: h_{CAS} / h_{CEA} > \delta$$

   $$H_A: h_{CAS} / h_{CEA} \leq \delta$$

That is, the null hypothesis is that the hazard ratio is greater than some constant δ (stenting raises the risk by at least δ), while the alternative hypothesis is that the risk in stenting relative to surgery is less than δ.

3. An attempt to confirm the results of the primary analysis and to understand the learning curve involved in the procedure will be made by contrasting event rates in the lead-in series (all CAS patients) with the CAS and CEA patients in the randomized series in two separate analyses.

   a. The first of these analyses will focus on a non-randomized comparison of treatment differences made after covariate adjustment for the major prognostic factors including symptomatic status, age, gender, degree of stenosis and major comorbid conditions.

   b. The second of these analyses will take a propensity score approach to assess differences between treatment groups after adjustment for a propensity score developed to reflect the likelihood of receiving the two treatments.

Additional analyses that will be performed as part of the regulatory analysis, include specifically:

4. Examination of the following interaction terms for the primary endpoint event rate:

   a) gender and

   b) asymptomatic status (i.e., recently asymptomatic vs. always asymptomatic)

5. Evaluation of treated segment by ultrasound at 6 and 12 months.

3.0.4. Assumptions

Table 1: Anticipated event rate in strata defined by symptomatic status	Length of Follow-up		
	30 Day	1 Year	2 Years
Symptomatic	6.80%	8.24%	9.78%
Asymptomatic	4.35%	5.29%	6.30%
Combined (50-50)	5.58%	6.76%	8.04%

There is relatively more information available on the anticipated event rates for the CEA arm of the study. Assumptions for event rates in the symptomatic series were based on NASCET study and are generally supported by data available from the lead-in series. In symptomatic patients in NASCET the peri-procedural event rate was 5.8%, and the post-procedural event rate was 1.68%. Based on data becoming available in the lead-in series of CREST, for purposes of these calculations we are assuming, that an additional 1% of the patients will suffer a peri-procedural MI, bringing the peri-procedural event rate to 6.8%. These rates can be used to calculate the probability of an event by one year ($1 - (1-0.0680)*(1-0.0168)^{11/12} = 0.0824$), and at two years ($1 - (1-0.0680)*(1-0.0168)^{(1+11/12)} = 0.978$), which are shown in Table 1.

A peri-procedural event rate of 3.35% is estimated in the asymptomatic population in the CEA arm based on the paper by Rothwell (Stroke 1996; 27:266-269), again with an assumed 1% MI rate the peri-procedural event rate for asymptomatic patients was assumed to be 4.35%. We have assumed the same ratio of post-procedural events to pre-procedural events for the asymptomatic patients as seen in NASCET for symptomatic patients, reflecting a rate post-procedural event rate of 1.07%. These rates can be used in formulas similar to the symptomatic group to provide anticipated event rates at 1 and 2 years for the asymptomatic group.

The event rate for the composite population of symptomatic and asymptomatic patients is then a function of the proportion of each patient type. Conservatively, we assume a 50-50 mix of symptomatic and asymptomatic patients, with an average event rates also shown in Table 1.

3.0.5. Analysis Approaches

3.0.5.1. Primary Regulatory Analysis

Under the assumptions above, the primary regulatory analysis (as described in 3.0.1) will be an assessment of an equivalency analysis contrasting the pooled asymptomatic and symptomatic populations. In this analysis a one-sided 95% confidence limit will be calculated for the difference in event rates at one year (which will be calculated from Kaplan-Meier estimates with Greenwood variance estimates). The difference in the event rate will be calculated under the assumption that the estimated rates are normally distributed. Conservatively, assuming a 50-50 mix by symptomatic status (from Table 1 implying an event rate of 6.76%) and with a sample size of 2500 patients, a δ of 2.5% can be supported with 80% power and the power increases to approximately 82% with a δ of 2.6% [Blackwelder. CCT 1982;3:345-353].

Secondary Analyses

The interaction of symptomatic status on results (3.0.2, item #1) will be assessed using a difference hypothesis format (i.e., the null hypothesis is that the interaction is not present, in contrast to the alternative that it is present). Like the primary analysis, event rates will be calculated using Kaplan-Meier estimation for the four groups involved in the interaction ($CEA_{Asymptomatic}$, $CEA_{Symptomatic}$, $CAS_{Asymptomatic}$, and $CAS_{Symptomatic}$) and differences will be tested under the assumption of normality. Strata-specific estimates will be considered if the p-value for this test is in the neighborhood of 0.1 (or less).

Regardless of the outcome of the assessment of interaction, strata-specific estimates will be produced for the symptomatic and asymptomatic patients (3.0.2, item #1). This contrast will be made in the equivalency hypothesis format. The appropriate δ is a function of both the anticipated event rates (see Table 1) and the achieved sample size (that will not be known until the closure of data). As can be seen in Table 2, if the anticipated recruitment of 1400 symptomatic patients is achieved, a δ of 3.7% can be supported to assess differences at 1-year with 80% power in the symptomatic strata. Likewise, if the anticipated recruitment of 1100 asymptomatic patients is achieved, a δ of 3.4% can be supported to assess differences at 1-year with 80% power in the asymptomatic strata . The exact δ employed in the analysis will be determined by the achieved sample size in each strata.

Table 2: δ to be used in analysis as a function of achieved sample size

	Symptomatic	Asymptomatic
800	4.8%	3.9%
900	4.6%	3.7%
1000	4.3%	3.5%
1100	4.1%	3.4%
1200	3.9%	3.2%
1300	3.8%	3.1%
1400	3.7%	3.0%
1500	3.5%	2.9%
1600	3.4%	2.8%
1700	3.3%	2.7%

In addition to assessing differences between CAS and CEA treatment groups at 1-year, an equivalency approach will be used to assess difference in treatment groups during the 30-day peri-procedural period (3.0.2, item #2). Statistically, an approach identical to the assessment of the primary analysis will be employed. The assessment of the equivalence at 30-days is straightforward, and with the anticipated 5.58% event rate a δ of 2.3% can be supported with 80% power.

Analysis of the long-term durability of the stent will be assessed by proportional hazards analysis (3.0.3, item #2). Since review of the literature and available software did not provide direct approaches for calculations, simulation approaches were taken to establish the δ that can be supported by CREST. The general approach is to assume the distribution of events is "equivalent" for CAS and CEA, and then determine the distribution of the upper limit of the 95% one-sided confidence limit for the estimated hazard ratio. The appropriate δ associated with x% power is then the point where x% of the confidence intervals fall below. This was determined by a simulation approach.

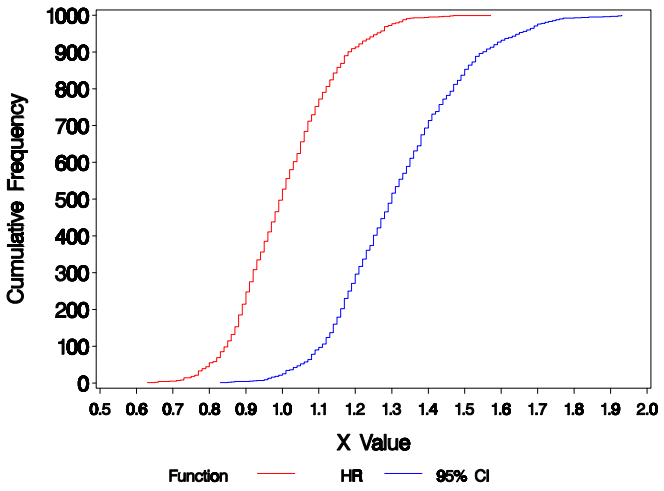
Table 3: Recruitment by year with anticipated length of follow-up	Patients Recruited	Percent of Sample	Average Follow-up (Years)
2000-Q1/Q2	0	0%	5.00
2000-Q3/Q4	2	0%	5.00
2001-Q1/Q2	2	0%	5.00
2001-Q3/Q4	6	0%	5.00

2002-Q1/Q2	1	0%	5.00
2002-Q3/Q4	14	1%	5.00
2003-Q1/Q2	37	1%	5.00
2003-Q3/Q4	76	3%	4.75
2004-Q1/Q2	108	4%	4.25
2004-Q3/Q4	125	5%	3.75
2005-Q1/Q2	364	15%	3.25
2005-Q3/Q4	422	17%	2.75
2006-Q1/Q2	445	18%	2.25
2006-Q3/Q4	445	18%	1.75
2007-Q1/Q2	453	18%	1.25

The events under both treatments were generated under a piecewise exponential distribution, allowing a reflection of the higher event rate during the 30-day peri-procedural period followed by the lower event rates during the extended post-procedural period. During the first 30 days (or 0.0822 of a year) a λ of 1.43 was assumed, reflecting the 5.8% event rate. For the remaining 5 years, a λ of 72.2 was assumed, reflecting the 1.38% event rate.

Finally, the anticipated pattern of recruitment, and the implied length of the follow-up is provided in the Table 3. As can be seen (and similar to other endarterectomy studies), the majority of patients will have relatively short follow-up

A total of 1000 simulations were run under the alternative hypothesis of equivalence (i.e., the same parameters for both the CEA and CAS groups) for the anticipated sample size of 2,500 patients. The results of these simulations are shown in the cumulative frequency for the hazard ratio and the one-sided upper 95% confidence limit (see figure). From these results, a δ of 1.47 is associated with the 80% percentile of for the one-sided 95% confidence limits, and would represent the definition of "equivalence" in this format.



The final two secondary analyses (Analyses identified in 3.0.3, items #3a and #3b) will contrast the event rate from the lead-in series to that observed in the CEA patients from the randomized study. In the first of these analyses (3.0.3, #3a) will focus on differences between treatment groups after adjustment for potential confounding factors. Because this is a non-randomized contrast, covariance adjustments for differences in patient characteristics are made prior to any contrast. Additionally, the varying levels of previous CAS experience among operators who performed lead-in cases may have to be considered in the analysis. Because of the survival nature of these data, and the need for this covariate adjustment, differences between treatment groups will be assessed using proportional hazards analysis. The lead-in series includes only one-year of patient follow-up. As such, all patients event-free at one year will be considered censored at that

point. Symptomatic status, age and the degree of stenosis are likely to be important prognostic factors – and adjustment for these factors will be made in the proportional hazards model contrasting treatment differences. In addition to these *a priori* adjustments, an assessment of other prognostic factors will be made within the lead-in series, and these prognostic factors will be added to the *a priori* factors in a secondary analysis. The event rate at one year is anticipated to be 6.76%, implying that 84 events should occur within those 1250 patients randomized to CEA. It is not clear how large the sample size for the lead-in series will be; however, it is highly likely to be at least 1800 patients, and assuming a similar event rate implies an additional 122 events in this series. With a total of 206 events (84+122), a hazard ratio of approximately 1.49 can be detected with 80% power with an α of 0.05. [Schoenfeld DA. Biometrics 1983;39,499-503].

The second analysis (3.0.3, #3b) will assess differences between treatment groups after adjustment for a propensity score developed to reflect the likelihood of receiving the two alternative treatments. This propensity score will be developed using logistic regression, where the outcome will be whether the patient receives the CAS procedure (i.e., is in the lead-in) as compared to receiving the CEA procedure (i.e., is part of the randomized series and assigned to the CEA procedure). It is anticipated that the predictive variables will include demographic factors (age, race, sex), measures of disease severity (symptomatic status and percent stenosis), and concomitant diseases (major stroke risk factors including previous heart disease, previous stroke, diabetes, and smoking). Patients will be stratified into 5 groups or less, corresponding to equally-spaced probabilities of receiving the CAS procedure. Indicator variables corresponding to these strata will be entered into a proportional hazards analysis assessing differences between the lead-in CAS patients and the randomized CEA patients. Care will be taken to ensure that the treatment effect is consistent across propensity strata (i.e., there is no strata-by-treatment interaction). Restrictions to the analysis (limitations to one year follow-up) and power to detect differences is identical to methods above.

For the other secondary analyses (acute success, target lesion revascularization at 12 months, access site complication requiring treatment, cranial nerve injury unresolved at 1 and 6 months, evaluation of treated segment by ultrasound at 6 and 12 months), each outcome is dichotomous (yes or no for each patient) or ordinal and the primary analysis will focus on estimating the proportion of patients with the trait. With approximately 1250 participants in each arm of the trial, these proportions can be estimated with a 95% confidence limit smaller than $\pm$ 2.8%, providing a highly precise estimate of the trait.

3.2 Analysis for Lead-In/Credentialing Phase

As part of the lead-in/credentialing phase, CREST Investigators will be required to perform up to approximately 20 stent implantations as designated by the CREST IMC. These data will be evaluated by center, and reviewed by the IMC prior to center certification. Additionally, when analyzed in total, these data can be used to establish the risk of an "event" associated with the placement of a stent. While there is flexibility in the definition of "event" for the primary analysis of the safety of this run-in period, we

propose the same definition as for the major CREST trial – death, any stroke (regardless of hemisphere), or myocardial infarction within the first 30 days.

It is anticipated that for each operator, the event rate will be higher for those stents placed early, and with increased operator experience the event rate will decline to a plateau. The systematic collection and reporting of these procedures will allow the estimation of shape of the "learning curve," and provide information on anticipated asymptomatic event rate (as well as the number of stents to be placed as part of a training program to reach this rate). In addition, these data can be used to identify operators with high event rates. In order to ensure the best operators in the CREST trial, the performance of these operators with high event rates should be under close scrutiny prior to permitting them to perform study procedures.

The probability of peri-procedural events can be estimated using Generalized Estimating Equations (GEE) with a binomial link function. This probability can be estimated as a function of: (1) the sequence number (1^{st} to 20^{th}) of the stent and (2) the individual operator. The estimate of the risk associated with each operator reflects the likelihood of events associated with that individual operator, and incorporates an appropriate adjustment for the stent sequence. This estimate will play a central role in identification of operators with "high" event rates and will guide the subsequent review of these individuals for acceptance into the CREST trial.

In addition, the approach provides an estimate of the probability of events as a function of the sequence number of the stent (from 1^{st} to 15^{th}). This detailed description of this "learning curve" is useful for several reasons. First, if the risk of an event does plateau, then further training beyond this plateau is not necessary. For example, if there is no evidence of a decline in the risk of an event between the 10^{th} and 20^{th} stent placed, the training of future operators may be limited to placing only 10 stents. In addition to providing a description of the shape of the learning curve, the approach also provides an insight to the anticipated peri-procedural event rate after training. Specifically, if there is evidence of the event rate plateauing, then the estimated event rate at the end of the training program (e.g., the 20^{th} stent) provides an indication of the anticipated event rate after the training program. Importantly, this estimate is not falsely inflated by the anticipated higher event rate early in process of placing stents. The precision of this estimate of the event rate is a function of the level of the within-operator correlation, with higher within-operator correlations implying an increased ability to "improve" the estimate of the event rate for the 20^{th} stent using information from stents 1-19. Since the degree of with-in operator correlation is not known, the exact precision of this estimate is unknown. However, in the worst case (that is not anticipated to occur), there will be no correlation within-operator and the event rate at the 20^{th} stent will be based on information from that stent alone. In this worst case scenario, the precision would be identical to basing the estimate on data from that sequence number alone, which is to calculate the simple binomial likelihood of an event on the 20^{th} stent from the 40 to 60 operators. In this worst case, the observed event rate was 10%, the 95% confidence limits on this rate would be ± 7.6%. We anticipate the precision of this estimate will be substantially improved by the introduction of a sizable within-person correlational structure.

As such, the approach provides several important estimates. First, it provides an overall estimate of the proficiency of each operator, allowing for the identification of operators likely to have high event rates. These operators will be closely examined prior to permitting their inclusion of data to the study. Second, it provides a description of the shape of the "learning curve". This permits informed decisions to be made as to how many stents will be required as part of a training program. Finally, it provides an estimate of the peri-procedural event rate that is likely to be experienced, a first step in establishing the safety of the procedure.

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APPENDIX F HOW TO MEASURE CAROTID STENOSIS BY NASCET CRITERIA

The accuracy and reproducibility of the angiographic endpoints of this protocol are dependent upon each investigator's commitment to rigorous image acquisition techniques. Most centers involved in this protocol have participated in one or more prior angiographic trials that have emphasized the importance of obtaining high quality angiograms. For those other centers, a gentle reminder that adherence to strict acquisition guidelines will ensure low observer variability and high quantitative precision.

Special Considerations for Image Acquisition:

- Please make certain that all images forwarded to the Angiographic Core Laboratory with appropriate labeling that will include the site number, patient ID number, and date of the procedure
- We also need the Technologist Worksheet (with the calibration source diameter) and Catheterization Report
- Make certain that the image sets that have qualified the patient for CREST are forwarded to the Core Laboratory
- For digital prints, please place two image per page with appropriate labels
- DICOM3 compatible CDs are preferred

Image Calibration:

Although a contrast filled injection catheter or sheath can be used for image calibration, **radioopaque markers or a ruler** are preferred. Please place the calibration object adjacent to the carotid artery, but make certain that it does not overlap the vessel. Include the size of the object on the Technician Worksheet

NASCET Measurement of % Diameter Stenosis:

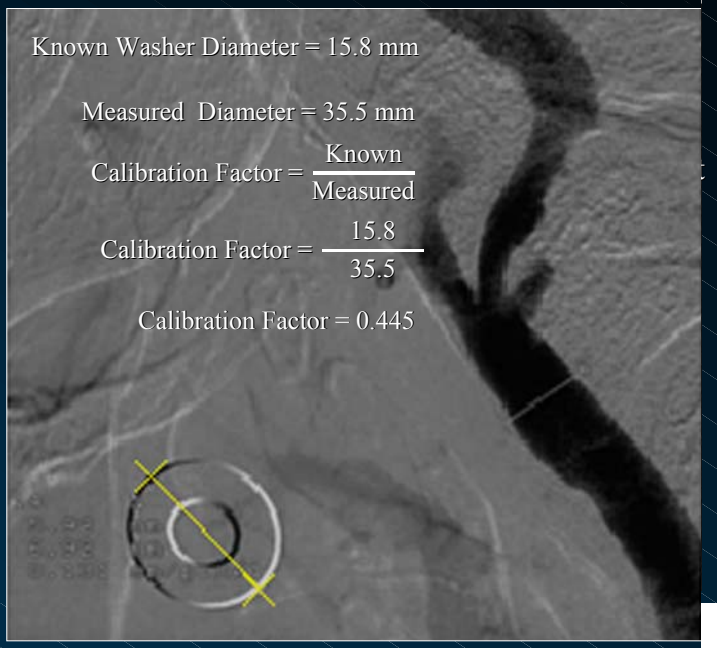
This study will utilize the NASCET method for determining percent stenosis in the target ICA. With this method, the angiographic view showing the greatest degree of narrowing is used to take two measurements: (a) the luminal diameter at the point of greatest stenosis and (b) the diameter of the normal ICA distal to the lesion. Percent diameter stenosis (S) is calculated with the following formula: $S = 100 – (a/b \times 100)$.

NASCET Measurement of % Diameter Stenosis

NASCET Method

Image Calibration

- Note the known washer diameter
- Measure the washer using a digital caliper or ruler
- Determine the calibration factor using the listed formula
- The calibration factor will be multiplied by the measured arterial diameter to determine the actual vessel diameter



NASCET Method

Image Calibration

- Measure the internal carotid artery using a ruler or digital caliper
- Multiply this number by the calibration factor to determine the internal carotid diameter
- Repeat the same measurement for the minimal lumen diameter
- Use the formula provided to calculate the % diameter stenosis